IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS
Patent Owner.

Case IPR2019-00741
U.S. Patent No. 9,732,149

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,732,149

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

Amgen Inc. petitions for *Inter Partes* Review, seeking cancellation of claim 1, the sole claim, of U.S. Patent No 9,732,149 ("the '149 patent"; AMG1001), assigned to Alexion Pharmaceuticals, Inc. ("Alexion"). Claim 1 is unpatentable under 35 U.S.C. §§ 102 and/or 103. This Petition is supported by the expert declaration of Dr. Joseph Balthasar (AMG1002), an expert in the development and evaluation of therapeutic monoclonal antibodies. *Id*., ¶¶1-10. Because the petition demonstrates a reasonable likelihood that claim 1 is unpatentable, institution is warranted.

II. Introduction.

Claim 1 of the '149 patent claims an antibody having a specific sequence that binds C5. During prosecution of the parent patent, Alexion asserted—incorrectly—that the claimed sequence "was not disclosed in the prior art; nor was it available to the public." AMG1014, 586-588. 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]." AMG1015, 772. But, as shown herein long before the '149 patent's alleged priority date, Alexion repeatedly published the claimed anti-C5 antibody.

Alexion admitted that it performed at least 17 clinical trials treating paroxysmal nocturnal hemoglobinuria ("PNH") with a humanized anti-C5 antibody ("eculizumab"), and that the antibody used in those trials had the claimed amino acid sequence. *Id.* 735-738. Thus, by Alexion's admission, prior art publications of those trials necessarily disclose the claimed sequence, inherently anticipating the challenged claim. 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 as claimed, with a reasonable expectation of success. The challenged claim, therefore, offers 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 to Evans et al. ("Evans"), which is prior art to the '149 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 meanwhile Alexion did not inform the UPSTO that it had been repeatedly publishing on eculizumab, methods of using it to treat PNH, and its amino acid sequence—including its engineered IgG2/IgG4 heavy chain—years before filing the '606 application. Indeed, Alexion proudly boasted about widespread knowledge of the IgG2/IgG4 constant region in the art when it suited Alexion's interests, but it remained silent about it to the USPTO. AMG1049, 838-839. Thus, Alexion's carefully timed pursuit of the '606 application one day before product approval improperly 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 of eculizumab. Indeed, Alexion itself admitted, prior to that date, that eculizumab was the subject of at least 17 different clinical trials, many of which were published. The table below

[1] The '149 patent claims priority to the '606 application.

summarizes Alexion's prior art public disclosures of the claimed antibody:

Table 1 – Publications Disclosing the Claimed Antibody (Eculizumab)

Study	**Alexion Study Number[2]**	**Exemplary disclosure**
Hillmen (AMG1004) Phase 2 Pilot Study[3] 11 patients	C02-001	"In this trial, we investigated whether *eculizumab* could reduce the incidence of intravascular hemolysis, hemoglobinuria, and transfusion requirements in patients with PNH." AMG1004, 553.
Hill '05 (AMG1047) Phase 2 Pilot Study Extension #1 11 patients	E02-001	"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 '04 (AMG1011) Phase 2 Pilot Study Extension #2 10 patients	X03-001	"We now report that 10 of the 11 patients from the initial 3 month study have continued to receive 900 mg *eculizumab* every other week for 2 years." AMG1011, Abstract.

[2] Study numbers as identified in Alexion's statements made to the USPTO during prosecution. *See, e.g.*, AMG1015, 728, 736.

[3] 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 – Publications Disclosing the Claimed Antibody (Eculizumab)

Study	Alexion Study Number[2]	Exemplary disclosure
Bell (AMG1005) Summary of Pilot Study and Extensions 11 patients	N/A	"The specific anti-C5 antibody used in the study was *eculizumab*." AMG1005, ¶[0082].
Hillmen '06 (AMG1012) Phase 3 "TRIUMPH" study 87 patients	C04-001	"We report the results of the phase 3 Transfusion Reduction Efficacy and Safety Clinical Investigation, a Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using *Eculizumab* in Paroxysmal Nocturnal Hemoglobinuria (TRIUMPH) study…." AMG1012, 1234.
Young (AMG1013) Phase 3 "SHEPHERD" study 97 patients	C04-002	"SHEPHERD, an open-label, non-placebo controlled 52-week phase III clinical stud y, is underway to evaluate the safety and efficacy of *eculizumab* in a broader PNH population including patients with significant thrombocytopenia and/or lower transfusion requirements." AMG1013, Abstract.

Alexion also admitted to the USPTO that the eculizumab used in these trials necessarily has the claimed amino acid sequence. AMG1015, 738(¶6), 736. Thus,

by Alexion's admission, the humanized anti-C5 antibody administered in these published trials (eculizumab) necessarily has the claimed sequence, and the published eculizumab trials anticipate claim 1.

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 eculizumab as claimed, rendering claim 1 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 and used eculizumab as the starter "scaffold" antibody for creating a recombinant thrombopoietin (TPO) mimetic 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 sequence, LPIEGPTLRQWLAARAPV. 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[4] (another Alexion

[4] Alexion patent application publication US 2005/0191298 A1 ("Bell") also

patent) for more information on 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."[5] *Id*., ¶[0191]. As Dr. Balthasar explains, the skilled artisan would have readily identified the eculizumab heavy chain CDR3 sequences in Evans, thereby obtaining the complete amino acid sequence of the claimed antibody. *See* AMG1002, ¶¶52-53.

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, and that they can be combined with hybrid IgG constant domains to form a complete antibody. AMG1007, 44:4-13, 45:24-33; AMG1002, ¶¶14, 123-135. With the heavy and light chain variable region sequences in hand, the artisan would have needed only to 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).

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explicitly cites and incorporates by reference Evans for preparing eculizumab. AMG1005, ¶[0052].

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

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 antibodies—as a control antibody. *Id*., 12:35-37, Fig. 15. Mueller provided the amino acid sequences of eculizumab's IgG2/IgG4 heavy chain constant region and light chain constant region. *Id*., 52-53, 58-61; AMG1002, ¶55. Further, artisans knew well before March 15, 2007, that eculizumab contained a hybrid IgG2/IgG4 constant region because Alexion expressly disclosed this feature to the public at least as early as 2005. AMG1034, 1279. 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, ¶¶123-135.

Alexion admittedly placed the 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 make the anti-C5 antibody as claimed. The prior art also supplied sufficient information about the sequence and structure of eculizumab such that the artisan could and would have made the

antibody as claimed with a reasonable expectation of success. The challenged claim, therefore, offers 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 claim 1 of the '149 patent is unpatentable as anticipated and/or obvious.

IV. The '149 Patent and its prosecution history.

The '149 patent issued on August 15, 2017 and claims a priority date of March 15, 2007.[6] The '149 patent's sole claim recites:

> 1. An antibody that binds C5 comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

AMG1001, 39:2-4.

The '149 patent issued from U.S. Appl. No. 15/284,015, filed on October 3, 2016. During prosecution, the examiner initially rejected Alexion's claim as anticipated by Hillmen, which disclosed methods of using eculizumab for treating PNH, in view of the general knowledge in the art of eculizumab's sequence, as

[6] Petitioner does not concede that the '149 patent is entitled to any of its claimed priority dates.

reflected in references such as Thomas (AMG1023). AMG1015, 596-598. The examiner also rejected the claims as anticipated by (1) Appel et al., *Kidney International* 70, S45-S50, (2006), and (2) Wang et al., US2005/0271660. *Id*., 598.

In response, Alexion asserted—incorrectly—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*., 709. 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 rejections recite using an antibody [with the claimed sequence]." *Id*., 772.

As shown herein, the examiner was misled. And Alexion has repeatedly made these same misleading arguments to obtain additional eculizumab patents related to the '149 patent[7] that claim subject matter already in the public domain. For example, when prosecuting U.S. 9,725,504 (claiming methods of using

[7] 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).

eculizumab formulations), Alexion argued that the "complete structure of eculizumab was not disclosed in the prior art; nor was it available to the public" and that "none of these references even suggests the unique non-naturally occurring, protein-engineered heavy chain of eculizumab, which confers important, unexpected functional effects." AMG1014, 586-588. And when prosecuting U.S. 9,718,880 (claiming eculizumab formulations), Alexion again argued that "the complete structure of eculizumab was not disclosed in the prior art, nor was it available to the public." AMG1016, 179-180, 720.

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…."[8] AMG1017, 277, 291(¶5.1.2). And during prosecution of

[8] 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

related U.S. Application No. 11/127,438, Alexion argued that its provisional applications provided written description for claims to "eculizumab" and an 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).[9] 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.

Alexion's intent to disclose it to the public. AMG1054, 247-254, 292-293.

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

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

A. Humanized monoclonal antibodies were well-known.

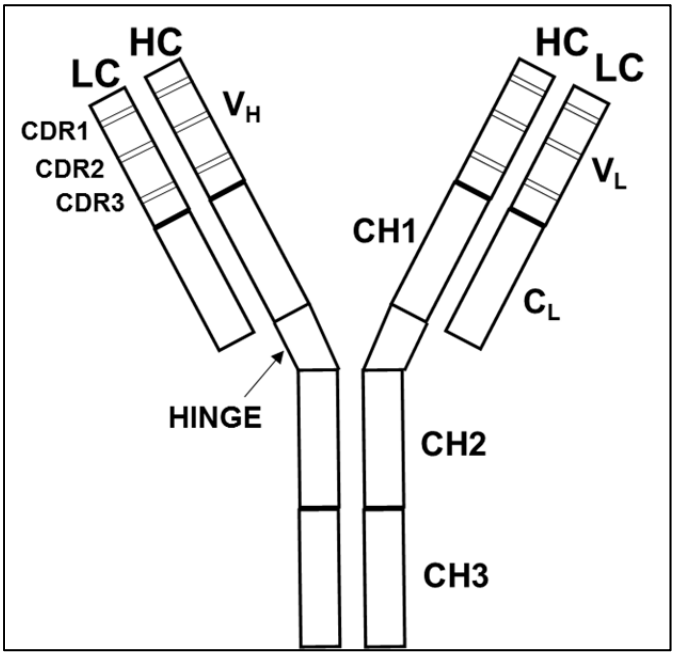
Before March 15, 2007, the structure of humanized monoclonal antibodies was well understood in the art. AMG1002, ¶¶20-26. Antibodies in general were known to be Y-shaped proteins made up of two identical "heavy chain" polypeptides and two identical "light chain" polypeptides. AMG1018, 7. The art taught 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" is used to refer to an antibody having a human framework into which CDR regions from a non-human monoclonal antibody (*e.g.*, a mouse antibody) are inserted into a human antibody framework. AMG1007, 5:57-67.

The constant regions of the antibody heavy chain provide different functional characteristics to the antibody. AMG1018, 8. Different antibody subclasses (e.g., IgG2, IgG4) can provide different functions based on the Fc receptors to which they bind. For example, IgG4 was known for its low propensity to activate the complement system. AMG1023, 1399. And recombinant antibodies

with a hybrid IgG2/IgG4 constant region have both a reduced ability to elicit unwanted inflammatory events and lessened propensity to activate complement. AMG1032, 11, 19, 28; AMG1031 ("Mueller II"), 451; AMG1002, ¶22.

A diagram depicting the basic antibody structure is shown below:



See AMG1002, ¶24.

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 well known as a humanized anti-complement (C5) monoclonal antibody derived from the mouse monoclonal antibody "5G1.1," and thus was frequently referred to as "h5G1.1" or "h5G1.1-mAb" in the art:

- Bell taught in 2005 that "[t]he antibody *h5G1.1-mAb* is currently

undergoing clinical trials under the trade name *eculizumab*." AMG1005, ¶[0052]; and

- Tacken taught in 2005 that the antibody "*h5G1.1-mAb*" is synonymous with "*5G1.1, eculizumab*, Alexion Pharmaceuticals." AMG1034, 1279; AMG1002, ¶¶27-48.[10]

Moreover, Alexion has admitted on the record 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, ¶¶42-48. Whereas therapeutic monoclonal antibodies are typically based on a particular antibody isotype constant region (*e.g.*, IgG2 or IgG4; *see e.g.,* AMG1040, 55), eculizumab was known to contain a hybrid constant region with portions of both IgG2 and IgG4. For example, Tacken explicitly described using "h5G1.1-mAb (5G1.1, *eculizumab*; Alexion Pharmaceuticals)" containing an "*IgG2/IgG4 constant region*." AMG1034, 1279.

[10] *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").

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." AMG1049, 838-839. As already discussed above, artisans knew 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, ¶22.

Even though the prior art contained other "humanized 5G1.1" antibodies, the skilled artisan would have been able to readily distinguish eculizumab from them based on whether a hybrid IgG2/IgG4 constant region was present. AMG1002, ¶47. For example, in 1996, Thomas *et al.* disclosed creating a humanized 5G1.1 antibody containing the same CDR regions as the original murine 5G1.1 antibody used to make eculizumab. AMG1023, 1389. Thomas' antibody, however, was an "IgG4 isotype" called "h5G1.1 HuG4." AMG1023, 1396. A skilled artisan would have known that Thomas's "h5G1.1 HuG4" antibody, having an IgG4 constant region, was different than eculizumab, with its hybrid IgG2/IgG4 constant region. AMG1002, ¶47.

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

Before March 15, 2007, the art taught eculizumab's full amino acid

sequence. AMG1002, ¶¶49-58. In 2003, Bowdish described a peptide-antibody recombinant protein using eculizumab as the starter antibody and a TPO agonistic peptide (mimetic) 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 the entire eculizumab amino acid sequence with the exception of the eculizumab heavy chain CDR3 sequence (HCDR3).[11] AMG1006, ¶¶[0191]-[0193], Figures 13A-13B (SEQ ID NOs: 67 and 69); AMG1002, ¶¶50-51. But that HCDR3 sequence—the only piece of eculizumab not expressly described in Bowdish—was known in the art from Evans. Indeed, Bowdish explicitly cites and incorporates by reference Evans for methods of making eculizumab, stating: "[c]onstruction of 5G1.1 is described in [Evans], incorporated herein by reference."[12] AMG1006, ¶[0191].

Evans disclosed all six CDR regions of the original mouse 5G1.1 antibody, which are underlined in the sequences provided in Evans' Figures 18 and 19.

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[11] 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, ¶51; AMG1006, Figs. 13A-13B; AMG1045, 582.

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

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. AMG1002, ¶¶108-117. When combined, the "scaffold" sequences for the TPO-mimetic+h5G1.1 antibody in Bowdish and eculizumab HCDR3 in Evans together form an anti-C5 antibody that has the claimed sequence. AMG1002, ¶¶51, 99, 108-113.

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, ¶¶55-57. 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, ¶55. 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 domain. *Id*., 58-61; AMG1002, ¶¶55-57.

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

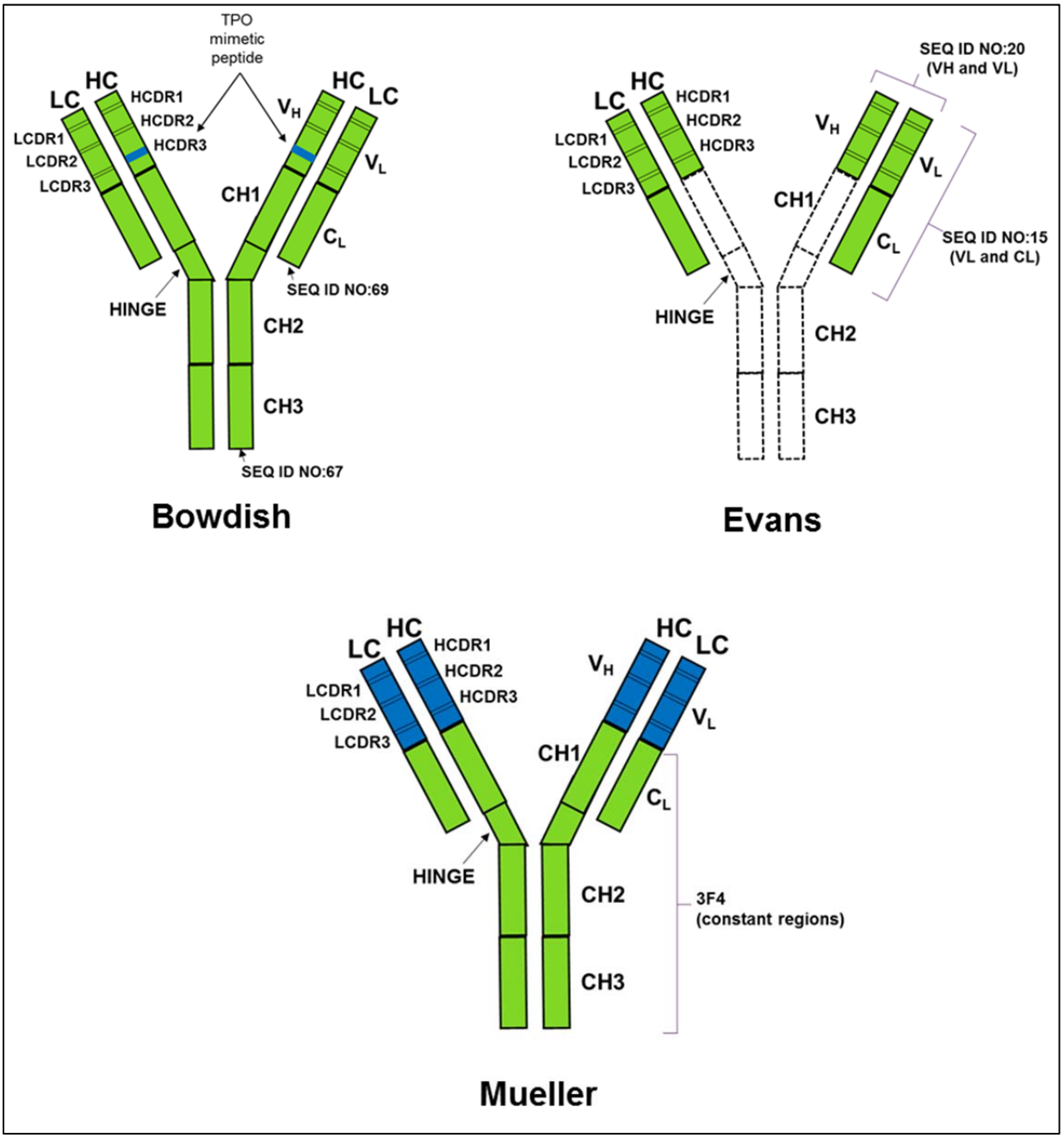

Figure 10.

See AMG1002, ¶58. In the above diagram, green represents the eculizumab

sequences disclosed in the reference, and blue represents non-eculizumab sequences in each reference. AMG1002, ¶58.

Though different portions of eculizumab's amino acid sequence were taught 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). Based on these teachings, the POSA would have had a reason to combine the references with a reasonable expectation of success as explained below in Sections XIII and XIV.

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 '149 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, ¶19. 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 '149 patent are plain on their face and require no further construction. AMG1002, ¶61. 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)	Claim	References
1	§102(b)	1	Hillmen

2	§102(b)	1	Hill '05
3	§102(b)	1	Bowdish
4	§103(a)	1	Bell, Bowdish, and Evans
5	§103(a)	1	Evans and Mueller

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

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

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

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

These references are prior art under 35 U.S.C. §102(b) because each published more than one year before March 15, 2007, the '149 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).

During prosecution, the examiner rejected Alexion's claims as (i) anticipated by Hillmen in view of Thomas; (ii) anticipated by Appel; and (iii) anticipated by Wang. AMG1015, 598-600. Those rejections rested solely on disclosures in Thomas and Evans for eculizumab sequence information. *Id.* The examiner later allowed the '149 patent claims mistakenly believing—because of Alexion's mischaracterization of the art—that the sequence and structure of eculizumab were not already known.

Though Hillmen was referenced by the examiner during prosecution, this Petition presents it in a different light, along with new references—Bell, Bowdish, and Mueller, which teach the IgG2/IgG4 constant domain missing from the art 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, this Petition presents important information that the examiner failed to appreciate or consider, including information never even presented to the examiner.

Consequently, this Petition is not the same as, substantially the same as, or cumulative of any previous arguments. Rather, 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.

Because the Grounds set forth herein provide new evidence, new combinations of art, and new arguments to address the erroneous bases through which Alexion obtained the '149 patent, § 325(d) does not preclude instituting this Petition.

X. Ground 1: Hillmen anticipates claim 1.

Hillmen anticipates claim 1. AMG1002, ¶¶70-77. 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).

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

Dr. Balthasar confirms that Hillmen disclosed all the limitations of claim 1, either expressly or inherently. AMG1002, ¶¶71-73. Hillmen expressly disclosed

"an antibody that binds C5" as claimed because Hillmen disclosed administering *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*…." AMG1004, Abstract. Hillmen further described eculizumab as an "*antibody against terminal complement protein C5*." AMG1004, Abstract. And 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—which was already in the public domain—necessarily possesses those very amino acid sequences.

During prosecution, Alexion submitted a list of eculizumab clinical studies—including Hillmen's Phase 2 Pilot Study (Study number "C02-001")—and affirmatively 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*." AMG1015, 738(¶6); *see also, id.*, 736 (study number "C02-001"). Alexion is bound by its admissions made during prosecution. *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, as claimed, 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 [patent at issue] claims something 'new' over the disclosure of the [prior art].").

Cases such as *Crish* are squarely applicable here and compel finding anticipation. Alexion admitted Hillmen necessarily disclosed the claimed antibody. The '149 patent's mere claim to the amino acid sequence that Alexion admits was a property of a prior art compound (eculizumab) contributes nothing over the prior art.

B. Hillmen's disclosure is enabling.

Hillmen also provided an enabling disclosure of the claimed antibody. 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.") An anticipatory reference must also "enable one skilled in the art to make the anticipating subject matter" without undue experimentation. *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 eculizumab having the claimed sequences. AMG1002, ¶¶74-76.

The alleged invention and single claim are directed to 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; AMG1015, 738(¶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 amino acid sequence. AMG1002, ¶¶42-58, 75-76.

Dr. Balthasar's Figure 10 above illustrates the art disclosing eculizumab amino acid sequences. *See* Section IV, *supra*; AMG1002, ¶58. 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, ¶75.

(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, ¶75.

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, ¶76. 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 eculizumab. And 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. Accordingly, Hillmen anticipates claim 1.

XI. Ground 2: Hill '05 anticipates claim 1.

Hill '05 also anticipates claim 1 because Hill '05 disclosed "an antibody that binds C5," eculizumab—a known antibody that necessarily possesses the claimed amino acid sequences. AMG1002, ¶¶78-87.

A. Alexion admitted that Hill '05's eculizumab necessarily has the claimed sequence

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. AMG1047, 2559-2560. 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. AMG1047, Abstract, 2560. For example, Hill '05 disclosed that patients in the extension study received "a maintenance dose of *eculizumab*." AMG1047, 2560. Hill '05 further described eculizumab as an "a *humanized monoclonal antibody* that specifically targets the *complement protein C5*." AMG1047, 2559. And Hill '05's eculizumab "comprises a heavy chain

consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4" because Alexion admitted that Hill '05's eculizumab necessarily possesses those very amino acid sequences .

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*." AMG1015, 738(¶6); *see also, id.*, 736 (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*." AMG1047, 2560; AMG1002, ¶¶79-83. 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]." AMG1015, 736.

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.

As already discussed, eculizumab was not new. Alexion serially published on eculizumab well before March 15, 2007. *See, e.g.,* AMG1004, Abstract, 554; AMG1042, Abstract; AMG1047, Abstract, 2560; AMG1011, Abstract; AMG1005, ¶¶[0081]-[0096]; AMG1012, Abstract, 1235; AMG1013, Abstract; AMG1002, ¶¶42-58. And merely claiming an inherent property of a known antibody —as Alexion claims in the '149 patent—does not confer novelty. *Crish*, 393 F.3d at 1258; *Atlas Powder*, 190 F.3d at 1347; *Abbott Labs.*, 471 F.3d at 1368.

B. Hill '05's disclosure is enabling.

Hill '05 is enabling for the same reasons discussed above in Ground 1. The alleged invention and single claim are directed to 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, ¶¶84-86. *See* Section 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, ¶85. 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, ¶86.

As in Ground 1, the law also compels finding anticipation in Ground 2. The claimed antibody was not new because Hill '05 taught 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 antibody without undue experimentation. *Donohue I*, 632 F.2d at 125; *Donohue II*, 766 F.2d at 533.

XII. Ground 3: Bowdish anticipates claim 1.

Bowdish anticipates claim 1 because Bowdish inherently disclosed the claimed "antibody that binds C5 comprising a heavy chain consisting of SEQ ID NO:2 and a light chain consisting of SEQ ID NO:4." AMG1002, ¶¶88-103.

A. Bowdish disclosed the claimed antibody.

Bowdish taught methods of making peptide-antibody recombinant proteins, and described using a 5G1.1 antibody as the starter "scaffold" antibody sequence for creating a recombinant TPO-mimetic+h5G1.1 antibody. AMG1006, ¶[0191]. Bowdish provided the full 5G1.1 antibody amino acid sequence except for the heavy chain CDR3 (HCDR3) sequence, which Bowdish replaced with the TPO-mimetic peptide sequence, LPIEGPTLRQWLAARAPV. AMG1006, ¶¶[0191]-[0193], Figs. 13A-13B, and SEQ ID NOs. 67 and 69; AMG1002, ¶¶89-93. As explained in more detail below, Bowdish's "5G1.1" starter antibody necessarily possessed the claimed sequences.

Bowdish provides the complete sequences of the heavy and light chains of the recombinant TPO-mimetic+h5G1.1 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, ¶¶91-92. Dr. Balthasar's Figure 3 below illustrates the structure of Bowdish's TPO-mimetic+h5G1.1antibody, showing the location of the TPO peptide (blue) in the

HCDR3 region of the polypeptide of SEQ ID NO:67 (heavy chain), and the polypeptide of SEQ ID NO:69 (light chain), where green represents the 5G1.1 "scaffold" sequences that are to SEQ ID NO:2 and SEQ ID NO:4:

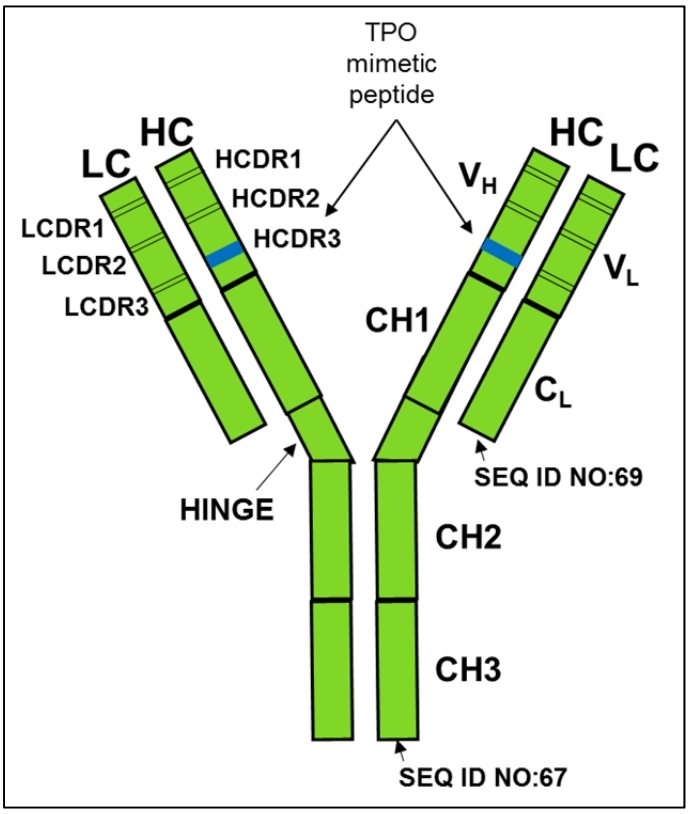

Figure 3.

AMG1002, ¶¶50, 92; 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 '149 patent's SEQ ID NO:4 as claimed; and the mature portion of Bowdish's SEQ ID NO:67 (i.e., the heavy chain) is 100% identical to the '149 patent's SEQ ID NO:2 as claimed, with the exception of the HCDR3 sequence. AMG1002, ¶¶96-100.

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, ¶91. Thus, the POSA would have known that the leader sequences in Bowdish's Figures 13A-13B are not part of the mature antibody sequence[13]. AMG1006, Figures 13A-13B; AMG1002, ¶91; AMG1045, 582.

A POSA would have understood that the only portion of the "scaffold" 5G1.1 antibody sequence not expressly disclosed in 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

[13] 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…." AMG1015, 546; *see Vitronics Corp.*, 90 F.3d at 1583; *Tyler Refrigeration*, 777 F.2d at 690.

replace the native CDR3." AMG1006, ¶[0191]; AMG1002, ¶¶91-93. Dr. Balthasar's Figure 3 above shows this, where green represents portions of 5G1.1 amino acid sequence present in Bowdish's TPO-mimetic+h5G1.1 antibody and blue represents the TPO-mimetic peptide sequence replacing the native HCDR3.

Bowdish's 5G1.1 "scaffold" antibody, therefore, inherently possessed a heavy chain of SEQ ID NO:4 and a light chain of SEQ ID NO:2 as claimed. Bowdish disclosed that the starter scaffold antibody 5G1.1 was produced according to Evans, stating that "[c]onstruction of 5G1.1 is described in [Evans], incorporated herein by reference."[14] AMG1006, ¶[0191].

Evans disclosed preparing different humanized C5-binding antibodies referred to as "5G1.1" antibodies. AMG1007, 19:47-49, 37:35-39:30, 40:31-45:4; AMG1002, ¶¶94-95. As Dr. Balthasar explains, a POSA would have understood that *all* 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, ¶95. Thus, a POSA would have known that the heavy chain of Bowdish's 5G1.1 starter antibody contained the YFFGSSPNWYFDV CDR3 sequence, regardless of which "version" of Evans'

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

humanized 5G1.1 the POSA considered. AMG1002, ¶95.

In view of the above, Bowdish's starter 5G1.1 antibody necessarily contained Evans' YFFGSSPNWYFDV HCDR3 sequence as its native HCDR3. AMG1002, ¶¶96-100. This is shown in Dr. Balthasar's Figure 12 below:

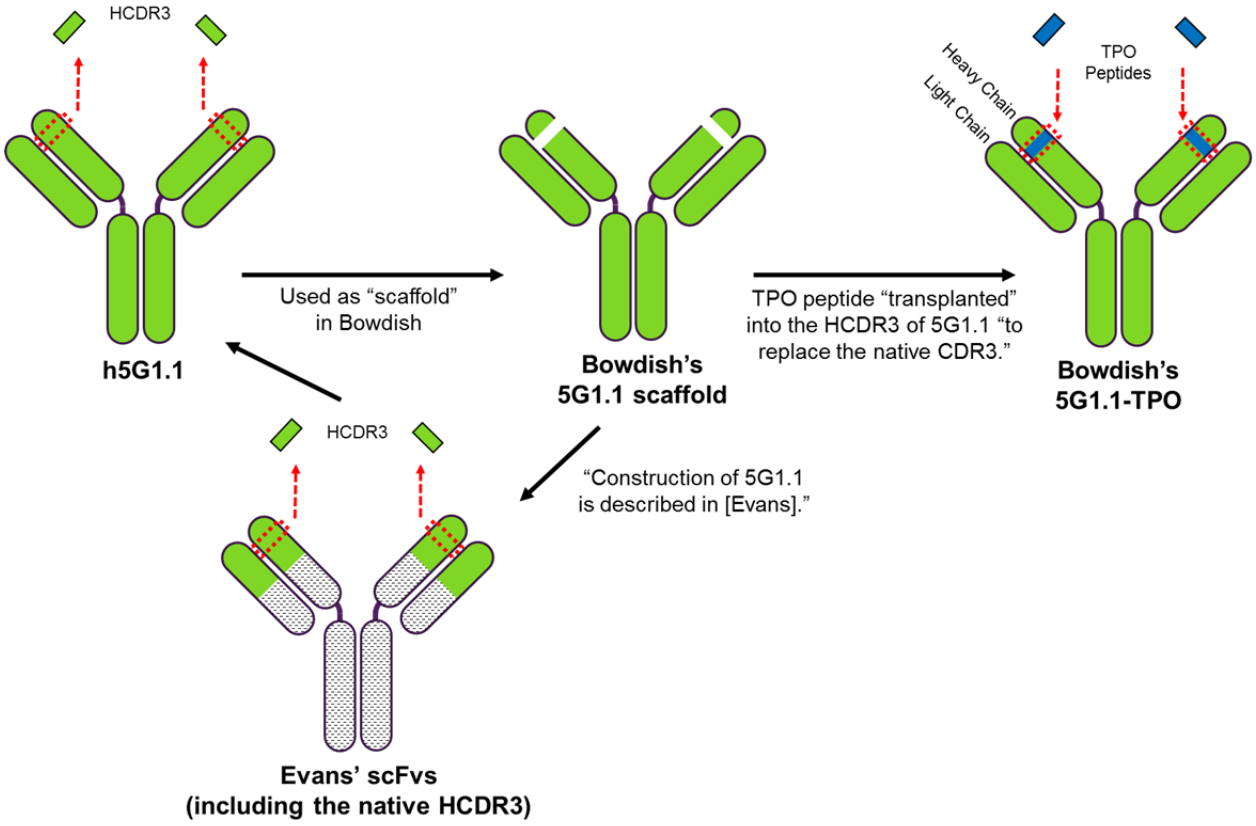

Figure 12.

Dr. Balthasar confirms that inserting Evans' HCDR3 sequence in place of Bowdish's TPO-mimetic peptide sequence in SEQ ID NO:67 creates an antibody heavy chain sequence that is a 100% match with SEQ ID NO: 2 from the '149 patent. AMG1002, ¶¶98-99. As already discussed above, Bowdish's light chain

SEQ ID NO:69 is a 100% match with SEQ ID NO:4 from the '149 patent. AMG1002, ¶100. Accordingly, Bowdish's disclosure of "5G1.1" as the starter scaffold sequence for creating a TPO-mimetic+h5G1.1 antibody is necessarily a disclosure of an anti-C5 antibody that binds C5 and has the claimed sequences. *MEHL/Biophile*, 192 F.3d at 1365.

B. Bowdish's disclosure is enabling.

Bowdish is enabling for many of the reasons discussed above in Grounds 1 and 2. AMG1002, ¶¶101-192. As Dr. Balthasar explains, a POSA would have known that Bowdish disclosed the entire amino acid sequence of the 5G1.1 starter antibody with the exception of the HCDR3 region, and that Evans disclosed the native HCDR3 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, ¶102; *see also, Donohue I*, 632 F.2d at 125; *Donohue II*, 766 F.2d at 533.

Given the narrow scope of claim 1 and the high level of skill in the relevant field, the POSA would have readily obtained the heavy and light chain sequences as claimed from the art using only routine experimentation. And, armed with the general knowledge in the relevant field, a POSA reading Bowdish would not have needed undue experimentation to gain possession of the claimed anti-C5 antibody. *Impax*, 545 F.3d at 1315-1316; *Wands*, 858 F.2d at 731; AMG1002, ¶102.

Bowdish therefore anticipates claim 1. AMF1002, ¶103.

XIII. Ground 4: claim 1 would have been obvious over Bell, Bowdish, and Evans.

Dr. Balthasar explains that a POSA reading Bell would have constructed an anti-C5 antibody by combining the 5G1.1 sequences taught in Bowdish and Evans. AMG1002, ¶¶104-113. And a POSA would have had reasons to combine these references with a reasonable expectation of success in arriving at the claimed antibody. AMG1002, ¶¶114-119. There are no objective indicia of nonobviousness. *See* Section XII.C.

A. Claim 1 would have been obvious.

1. Bell expressly taught all the limitations of claim 1 except eculizumab's amino acid sequence.

Bell disclosed "an antibody that binds C5" as claimed because Bell disclosed using "an *anti-C5 antibody* selected from the group consisting of *h5G1.1-mAb (eculizumab)*…" and also that the antibody "h5G1.1-mAb" was "undergoing clinical trials under the tradename *eculizumab*." AMG1005, ¶¶[0012], [0052] and [0082]. Bell described an anti-C5 antibody (eculizumab) clinical trial involving a 12-week "pilot study," followed by a 52-week extension study for a total of 64 weeks, followed by a second extension study for a total of two years.[15] AMG1005,

[15] Because the clinical study taught in Bell is the same C02-001 study in Hillmen and E02-001 study in Hill '05, which disclose the eculizumab amino acid

¶[0082]. The only information explicitly not recited in Bell is eculizumab's amino acid sequences (SEQ ID NOs: 2 and 4 as claimed), but these sequences were readily found in Bowdish and Evans. AMG1002, ¶107.

2. Bowdish and Evans taught the claimed amino acid sequences.

As already discussed in Ground 3, Bowdish described using a h5G1.1 antibody as the starter "scaffold" antibody sequence for creating a recombinant TPO-mimetic+h5G1.1 antibody. Bowdish provided the full h5G1.1 amino acid sequence except for the heavy chain CDR3 (HCDR3) sequence, which was replaced with the TPO-mimetic peptide sequence. AMG1006, ¶¶[0191]-[0193], Figs. 13A-13B, and SEQ ID NOs.:67 and 69; AMG1002, ¶¶108-110. And the missing HCDR3 sequence from Bowdish was taught by Evans. AMG1007, 44:12-13; AMG1002, ¶¶111-112. Dr. Balthasar's Figure 14 below depicts this

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sequences of SEQ ID NOs: 2 and 4, Bell, too, therefore anticipates claim 1 for the same reasons discussed above for Hillmen and Hill '05. AMG1015, 738(¶6); *see also, id.*, 736 (study numbers C02-001 and E02-001); AMG1005, ¶[0082]; AMG1002, ¶108. Hill '04 (study number X03-001), Hillmen '06 (study number C04-001), and Young '06 (study number C04-002) also anticipate claim 1 for the same reasons. AMG1015, 738(¶6), 736; *see also*, AMG1011, Abstract; AMG1012, 1235; AMG1013, Abstract; AMG1002, ¶108.

combination of art providing Bowdish's complete "scaffold" antibody sequence:

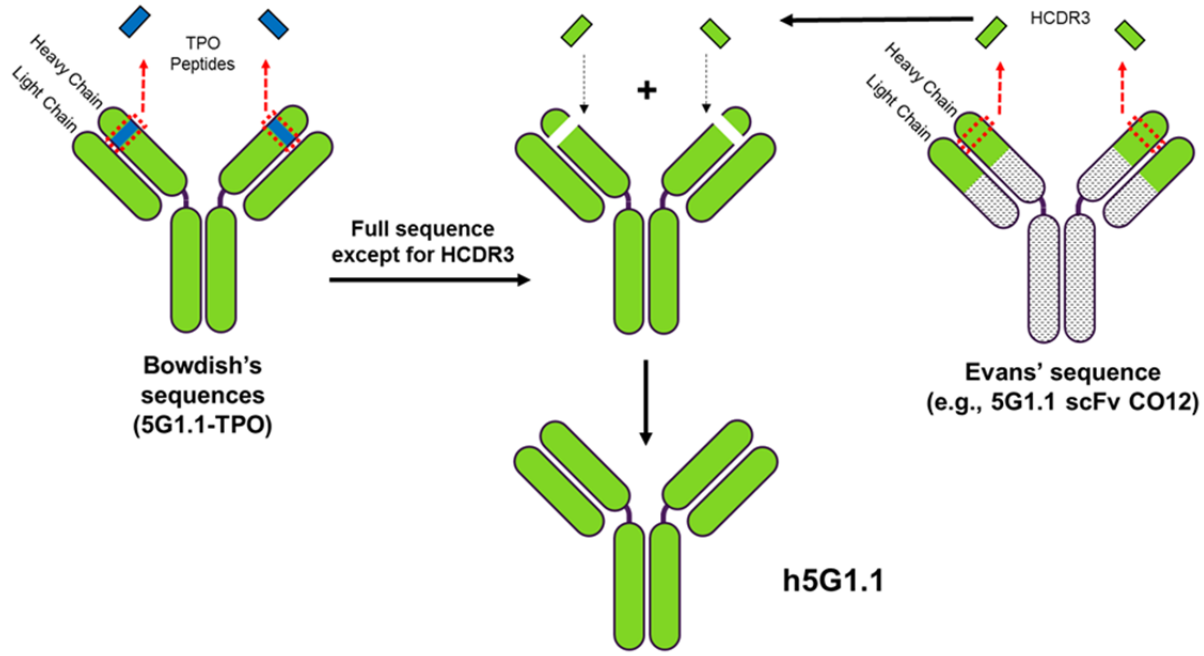

Figure 14.

AMG1002, ¶113.

Dr. Balthasar's Figure 3 (presented above in Ground 2) illustrates the structure of Bowdish's recombinant TPO-mimetic+h5G1.1 chimeric antibody, showing the location of the TPO-mimetic peptide (blue) in the native HCDR3 region of the polypeptide of SEQ ID NOs:67 (i.e., the heavy chain), and the polypeptide of SEQ ID NO:69 (i.e., the light chain), where green represents sequences 100% identical to SEQ ID NOs: 2 and 4 as claimed. AMG1002, ¶50; AMG1006, Figures 13A-13B. The missing HCDR3 piece, however, was taught in Evans, and Bowdish expressly directed a POSA to Evans. AMG1006, ¶[0191].

As already discussed, Evans disclosed a series of humanized 5G1.1 scFvs, and a POSA would have known that all of the heavy chain variable regions in Evans' scFvs contain the same YFFGSSPNWYFDV CDR3 sequence. 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, ¶111. Dr. Balthasar's Figure 14 above shows this, where Evans' HCDR3 sequence is extracted and inserted into Bowdish's construct. AMG1002, ¶¶112-113.

As Dr. Balthasar explains, a POSA would have expected that inserting Evans' YFFGSSPNWYFDV HCDR3 sequence in place of Bowdish's TPO-mimetic peptide sequence in SEQ ID NO:67 would provide the complete heavy chain sequence of the anti-C5 antibody. Indeed, Dr. Balthasar confirms that inserting Evans' HCDR3 sequence in place of Bowdish's TPO-mimetic peptide sequence[16] in SEQ ID NO:67 creates a heavy chain sequence that is a 100% match with SEQ ID NO: 2 from the '149 patent. AMG1002, ¶112. And as already discussed above, Bowdish's light chain SEQ ID NO:69 is a 100% match with SEQ ID NO:4 from the '149 patent. AMG1002, ¶112.

[16] To be clear, a POSA would have known that this would be achieved by replacing DNA encoding the TPO-mimetic (SEQ ID NO:65) with DNA encoding the HCDR3. AMG1002, ¶97.

3. 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 eculizumab (h5G1.1) is safe and effective for treating PNH patients, providing ample reason for a POSA to make a humanized anti-C5 antibody such as eculizumab. AMG1005, ¶¶[0083]-[0096]. Because Bell does not expressly provide the amino acid sequence of its anti-C5 antibody, a POSA would have looked to other known teachings in the art pertaining to eculizumab (5G1.1), like Bowdish and Evans.

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 Bell's anti-C5 antibody, 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, ¶¶114-115; AMG1005, ¶[0052]; AMG1034, 1279; *see also*, Section IV, *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 domain) as the starter antibody sequence when creating the TPO-mimetic+h5G1.1 antibody and further provided the amino acid sequence of the chimeric antibody. AMG1002, ¶¶115-116. Knowing that the only change made to the h5G1.1 amino acid sequence in Bowdish was replacing the original HCDR3 region in the scaffold h5G1.1 with a TPO-mimetic peptide, a

POSA seeking a humanized C5-binding antibody would have had reason to restore the original HCDR3 region to complete the eculizumab. AMG1002, ¶116.

The POSA would have looked to Evans for the missing HCDR3 sequence because both Bell and Bowdish explicitly direct the artisan to Evans for information on how each's h5G1.1 antibody was originally created. AMG1005, ¶[0052]; AMG1006, ¶[0191]; AMG1002, ¶116. For example, Bell stated: "[m]ethods for the preparation of *h5G1.1-mAb* [eculizumab] … are described in [Evans][17] … the disclosures of which are incorporated herein in their entirety by this reference." AMG1005, ¶[0052]. And Bowdish similarly stated: "[c]onstruction of *5G1.1* is described in [Evans], incorporated herein by reference."[18] 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

[17] Bell also cites Thomas. AMG1005, ¶[0052]. A POSA would not have chosen to combine Bowdish with Thomas' antibody over Evan's because Thomas's antibody is an IgG4 isotype, and not a human hybrid IgG2/IgG4 isotype, which was known to be less immunogenic and thus preferred over an IgG4 isotype. AMG1031, 448, 451; AMG1002, ¶¶46-47; *see also*, Section IV, *supra.*

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

peptide sequence in Bowdish's TPO-mimetic+h5G1.1 antibody with the HCDR3 sequence from Evans—to yield predictable results: a complete 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."); AMG1002, ¶117.

And, as Dr. Balthasar confirms by sequence alignment, the anti-C5 antibody obtained by replacing the TPO-mimetic peptide sequence in Bowdish's TPO-mimetic+h5G1.1 antibody with the HCDR3 sequence from Evans comprises a heavy chain consisting of SEQ ID NO:2 and a light chain consisting of SEQ ID NO:4 as claimed. AMG1002, ¶112.

A POSA would have reasonably expected to succeed in making the anti-C5 antibody as claimed because it would have required only basic molecular biology techniques to substitute Evans' HCDR3 sequence in place of Bowdish's TPO-mimetic peptide sequence. AMG1002, ¶118. A POSA also would have had an expectation of success in producing the anti-C5 antibody because antibody production methods were well-known in the art, and the antibody would be expected to bind C5. See, e.g., AMG1006, ¶¶[0130]-[0131]; AMG1002, ¶118.

Accordingly, claim 1 would have been obvious. And there are no objective indicia that support patentability. *See* Section XII.C., *infra*.

XIV. Ground 5: Claim 1 would have been obvious over Evans and Mueller.

Claim 1 also would have been obvious in view of Evans and Mueller. AMG1002, ¶¶120-137. Discussed below, a POSA would have had a reason to combine these references with a reasonable expectation of successfully making the claimed antibody. AMG1002, ¶¶123-128, 136-137. And no objective indicia support patentability. *See* Section XII.C.

A. Claim 1 would have been obvious.

1. Evans and Mueller disclose the claimed amino acid sequences.

As discussed in detail below, Evans disclosed the complete amino acid sequences of the heavy and light chain variable domains of anti-C5 antibodies. AMG1007, 44:4-13, SEQ ID NO:20; AMG1002, ¶¶121, 123-124, 129-131. And Mueller disclosed the amino acid sequence of an anti-C5 antibody's light chain constant domain and the hybrid IgG2/IgG4 heavy chain constant domain. AMG1008, 58-61; AMG1002, ¶¶121, 125, 132. Dr. Balthasar's Figure 16 below depicts this combination of art providing the complete anti-C5 antibody sequence:

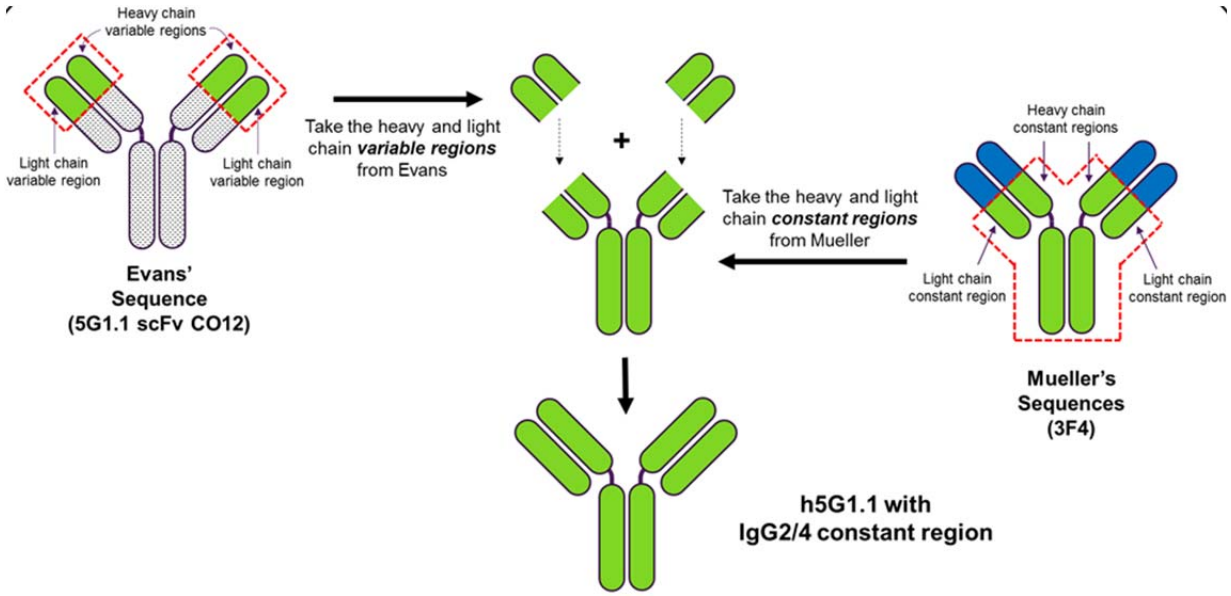

Figure 16.

See AMG1002, ¶133.

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, ¶124. 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[19] along with their amino acid

[19] A POSA would have known that a scFv comprises an antibody's light and heavy chain variable domains connected by a linker. *See, e.g.,* AMG1007, 6:39-41

sequences. *Id.* (construct numbers 2 and 11-18); AMG1002, ¶124. Evans also described combining the antibody variable regions with constant domains—including hybrid IgG constant domains—to make a complete anti-C5 antibody. AMG1007, 45:24-33.

In looking for a constant domain to pair with Evans' variable regions, a POSA would have looked to Mueller because Mueller taught antibody constant regions designed with a lower propensity to activate the immune system (and complement)—a desirable feature for a complement inhibiting antibody. AMG1008, 7:28-31, 8:23-26, 12:27-30; AMG1002, ¶¶125-128. A POSA reading Evans also would have looked to Mueller for "h5G1.1" sequence information because Mueller disclosed a 5G1.1 antibody with a hybrid IgG2/IgG4 constant domain. AMG1002, ¶¶125-128. 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

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("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, ¶124.

anti-C5 antibody because of the "h5G1.1" nomenclature coupled with the hybrid IgG2/IgG4 constant domain ("HuG2/G4"). AMG1008, 12:37, FIG. 15; AMG1005, ¶[0052]; AMG1034, 1279; AMG1049, 838-839; AMG1002, ¶¶54-55, 125-128.

As Dr. Balthasar explains, Mueller disclosed the amino acid sequence of a hybrid IgG2/IgG4 heavy chain constant domain when Mueller disclosed the sequence of the chimeric anti-VCAM "3F4" antibody. AMG1002, ¶¶129, 132; 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 16 above) and the constant regions of human hybrid IgG2/IgG4 (the green portions in Dr. Balthasar's Figure 16). AMG1002, ¶¶132-133; 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 16). AMG1008, Figure 9; AMG1002, ¶132. 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, ¶132.

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 15). AMG1008, 52-53, 56-57; AMG1002, ¶132. 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, ¶¶55, 125.

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 a 5G1.1 antibody, e.g., eculizumab. AMG1002, ¶¶45, 54-55, 125, 132. 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, ¶¶45, 54-55, 125, 132; 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 domain sequences obtained from

Mueller, a POSA would have looked back to Evans to complete the amino acid sequence of the anti-C5 antibody. AMG1002, ¶¶127-128. 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 no. 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, ¶¶127-128. This is shown in Dr. Balthasar's Figure 16 above, where the green portions depict Evans' heavy and light chain variable regions. AMG1002, ¶133; AMG1007, 44:4-13, SEQ ID NO:20.

That Evans taught additional 5G1.1 scFv constructs is of no moment 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 (1) a humanized heavy chain variable region of 5G1.1, (2) a linker, and (3) a humanized light chain variable region of 5G1.1. AMG1002, ¶¶124, 130; 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, ¶131. For example, 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, ¶131.

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." AMG1015, 546; 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, ¶131; AMG1048, 734 (Fig. 6).

Accordingly, a POSA would have understood that the mature light and heavy chain variable regions of Evans' anti-C5 antibody correspond to amino acids 3-111 and 127-248 of SEQ ID NO:20, respectively. AMG1007, 44:4-13; SEQ ID NO:20; AMG1002, ¶131.

Finally, a POSA would have expected that combining Evans' variable region sequences with Mueller's constant domain sequences[20] would provide the complete heavy and light chain sequences of an anti-C5- antibody. *See* Dr. Balthasar's Figure 16 above; AMG1002, ¶¶133-135.

As Dr. Balthasar shows by sequence alignment, the combination of eculizumab's heavy and light chain variable regions in Evans' SEQ ID NO:20 with Mueller's constant regions would make an anti-C5 antibody having SEQ ID NOs:2 and 4, as claimed. AMG1002, ¶¶134-135.

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

In seeking to make an anti-C5 antibody, a POSA reading Evans would have looked to Mueller because Mueller taught antibodies with constant regions designed with a lower propensity to activate the immune system (and

[20] 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, ¶97.

complement). AMG1008, 12:27-30; AMG1002, ¶¶125-126. Moreover, 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 anti-C5 antibody, *eculizumab*. AMG1002, ¶¶ AMG1002, ¶¶45, 54-55, 125.

Evans and Mueller taught complementary, familiar elements of anti-C5 antibody amino acid sequences. AMG1002, ¶¶129, 136. Thus, by combining familiar elements in the art according to known methods, the artisan would have predictably arrived at an 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, ¶136.

A POSA would have reasonably expected to successfully make an anti-C5 antibody as claimed because it would have required only basic molecular biology techniques to combine Evans' scFv variable regions with Mueller's constant

domains. AMG1002, ¶136. A POSA also would have had an expectation of success in producing an anti-C5 antibody as claimed because antibody production methods already were well-known. See, e.g., AMG1006, ¶¶[0130]-[0131]; AMG1002, ¶136.

B. 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 a related 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 claim and do not support non-obviousness. *Id.*

Moreover, Alexion's alleged results would not have been unexpected to a

POSA. AMG1002, ¶¶138-140. 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, ¶140. There is nothing unexpected here.

Petitioner is not aware of any other alleged objective indicia relevant to the '149 patent claim, and reserves the right to rebut any evidence Alexion asserts in this proceeding. *Amneal Pharms., LLC v. Supernus Pharms., Inc*., IPR2013-00368, Paper 8, at 12-13 (Dec. 17, 2013); AMG1002, ¶141.

XV. 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 (1) the '149 patent is available for IPR and (2) Amgen is not barred or estopped from requesting IPR of the '149 patent's single claim.

XVI. 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. 9,718,880 (IPR2019-00740) and 9,725,504 (IPR2019-00739), which are related to the '149 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).

XVII. Conclusion.

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

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C

Date: February 28, 2019
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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. 9,732,149 contains 11,154 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,
STERNE, KESSLER, GOLDSTEIN & FOX L.L.C.

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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. 9,732,149" 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. 9,732,149:

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