IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS
Patent Owner.

Case IPR2019-00739
U.S. Patent No. 9,725,504

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,725,504

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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 1-10 of U.S. Patent No 9,725,504 ("'504 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. *Id.*, ¶¶1-10.

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 '504 patent, Alexion asserted—incorrectly, yet repeatedly—that the claimed sequence "was not disclosed in the prior art; nor was it available to the public." AMG1014, 586-588, *see also* 739. 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*., 790. But, as shown herein, long before the '504 patent's alleged priority date, Alexion repeatedly published the claimed method of using a humanized anti-C5 antibody to treat PNH.

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.* 765-767. Thus, by Alexion's admission, prior art publications of those trials necessarily disclose the claimed sequence, inherently anticipating certain challenged claims. 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 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 '504 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— and its use for treating PNH years 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 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 the subject of at least 17 different clinical trials, many of which

[1] The '504 patent claims priority to the '606 application.

were published (summarized below in Table 1). AMG1014, 765-767. 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, ¶¶54-55.

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, ¶¶55, 183-185. 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).

Notably, Alexion *never* provided Mueller to the examiner. Published in

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[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.

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, ¶¶186-188. 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, ¶¶183-188.

Alexion admittedly placed methods of treating PNH using 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 use 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.

IV. The '504 patent and its prosecution history.

The '504 patent issued on August 8, 2017 from U.S. Appl. No. 15/260,888, and claims a priority date of March 15, 2007.[4] The '504 patent's sole independent claim recites:

> 1. A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

EX1001, 39:2-7.

Dependent claims 2-10 add certain limitations to this method. *Id.*, 39:8-32 Claim 2 requires administration by intravenous infusion ("IV"). Claim 3 requires dosing between 5 and 50 mg/kg. Claims 4-6 respectively require a single unit dosage form (claim 4) of 300 mg (claim 5), or a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative-free solution (claim 6). Claim 7 requires that the patient is anemic. Claim 8 requires a specific dosing schedule. Claims 9 and 10 require that the treatment results in a specified decrease in lactate

[4] Petitioner does not concede that the '504 patent is entitled to any of its claimed priority dates.

dehydrogenase levels.

During prosecution, the examiner initially rejected Alexion's claims 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 reflected in references such as Thomas (AMG1023). AMG1014, 557-558. The examiner also rejected the claims as obvious over (1) Hillmen, Thomas, and Evans or (2) Hillmen, Thomas, Evans, and US2005/0271660 ("Wang"). *Id*., 558-561.

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" 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." *Id*., 586-588. 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*., 790.

As shown herein, the examiner was misled. And Alexion has repeatedly made these same misleading arguments to obtain additional eculizumab patents

related to the '504 patent[5] that claim subject matter already in the public domain. For example, when prosecuting U.S. 9,732,149 (claiming eculizumab), Alexion 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. 9,718,880 (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…."[6] AMG1017, 277, 291(¶5.1.2). And during prosecution of

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[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).

[6] Alexion later tried to take this statement back during prosecution of a

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).[7] Alexion cannot have it both ways. Indeed, the European Opposition Division has already revoked at least two of Alexion's

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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.

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

European eculizumab-related patents. AMG1017, 368-378; AMG1027, 2667-2685.

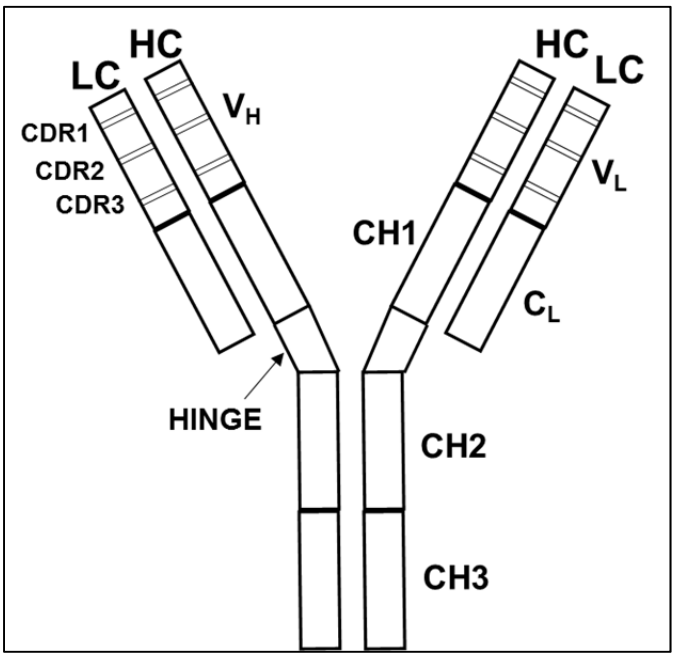
V. State of the art before March 15, 2007.

A. Humanized monoclonal antibodies were well-known.

Before March 15, 2007, the structure of humanized monoclonal antibodies was well understood in the art. AMG1002, ¶¶21-27. 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" 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, ¶25.

B. The prior art taught that PNH was associated with complement system dysregulation.

The complement system comprises a series of proteins that interact with one another in a cascade fashion as part of an immune response, serving a "complementary" role alongside the antibody immune response. AMG1022, R259. Before March 15, 2007, complement was well-understood to play a "central role in host defence against many micro-organisms and in the modulation of inflammatory reactions." *Id*. Complement system dysregulation was known to result in different pathological conditions, including PNH. AMG1023, 1389; AMG1002, ¶¶28-34.

PNH arises from a genetic mutation that depletes one or more cyto-protective proteins that prevent destruction of red blood cells ("RBCs"), platelets,

and other blood cells from complement-mediated attack. AMG1004, 553. PNH is characterized by hemolytic anemia (a decreased number of RBCs due to cell lysis), hemoglobinuria (hemoglobin in the urine due to RBC lysis), and hemoglobinemia (free hemoglobin in the bloodstream due to RBC lysis). AMG1005, ¶[0007]; AMG1002, ¶32.

C. Eculizumab was a known, effective treatment for PNH.

Eculizumab was already known to treat PNH. Alexion itself acknowledged that there were at least "17 different clinical studies using eculizumab that occurred prior to March 16, 2007." AMG1014, 764(¶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 IV 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. AMG1002, ¶¶35-42.

Table 1 – Clinical Trials Using Eculizumab to Treat PNH

Study	**Alexion Study Number**[8]	**Dosing Regimen**	**Outcome**
Hillmen (AMG1004) Phase 2 Pilot Study[9] 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" AMG1004, 554.	"safe and well tolerated in patients with PNH" "improvement in the quality of life in patients with PNH" AMG1004, Abstract.
Hill '05 (AMG1047) Phase 2 Pilot Study Extension #1 11 patients	E02-001	"maintenance dose of 900 mg intravenously every 14 days" for 52 weeks (64 weeks total) AMG1047, 2560.	"sustained reductions in hemolysis and blood transfusions and continued improvement in quality of life." AMG1047, 2565.
Hill '04 (AMG1011) Phase 2 Pilot Study Extension #2	X03-001	"10 of the 11 patients from the initial 3 month study have continued to receive 900 mg eculizumab every other week for 2 years."	"eculizumab is well tolerated and has persisting efficacy … as well as improvement in the symptoms of PNH, for over 2 years of

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

[9] 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[8]	Dosing Regimen	Outcome
10 patients		AMG1011, Abstract.	therapy." AMG1011, Abstract.
Bell (AMG1005) Summary of Pilot Study and Extensions 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." AMG1005, ¶[0082].	"reduction in adverse symptoms associated with PNH" AMG1005, ¶[0096].
Hillmen '06 (AMG1012) Phase 3 "TRIUMPH" study 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." AMG1012, 1235.	"Eculizumab is an effective therapy for PNH." AMG1012, 1233.
Young (AMG1013) Phase 3 "SHEPHERD" study	C04-002	"Eculizumab was dosed as follows: 600 mg IV every 7 days x 4; 900 mg 7 days later; and then 900 mg every 14±2 days."	"eculizumab treatment markedly reduces intravascular hemolysis, thereby providing clinical benefit to treated [PNH] patients."

Table 1 – Clinical Trials Using Eculizumab to Treat PNH

Study	Alexion Study Number[8]	Dosing Regimen	Outcome
97 patients		AMG1013, Abstract.	AMG1013, Abstract.

D. 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, ¶¶43-45.[10] Moreover, Alexion has admitted that "*h5G1.1* … [was] well-known to one of ordinary skill in the art *as eculizumab*…." AMG1049, 838.

[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").

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, ¶¶46-49. For example, Tacken explicitly described using "h5G1.1-mAb (5G1.1, *eculizumab*; Alexion Pharmaceuticals)" 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."[11] 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, ¶¶47, 57.

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[11] 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, ¶48.

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

Before March 15, 2007, the art taught eculizumab's amino acid sequence. AMG1002, ¶¶50-60. In 2003, Bowdish described a peptide-antibody recombinant protein using eculizumab as the starter antibody and TPO-mimetic as the agonistic 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).[12] *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.")[13].

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,

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[12] 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, ¶52; AMG1006, Figs. 13A-13B; AMG1045, 582.

[13] *See* note 5.

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, ¶¶139-142. When combined, the "scaffold" sequences in Bowdish and eculizumab HCDR3 in Evans together form a humanized anti-C5 antibody having the claimed sequence. AMG1002, ¶¶130-138.

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, ¶¶57-59. 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, ¶¶57-59. 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, ¶¶57-59.

Dr. Balthasar's Figure 10 below schematically shows which portions of eculizumab were disclosed in the prior art.[14]

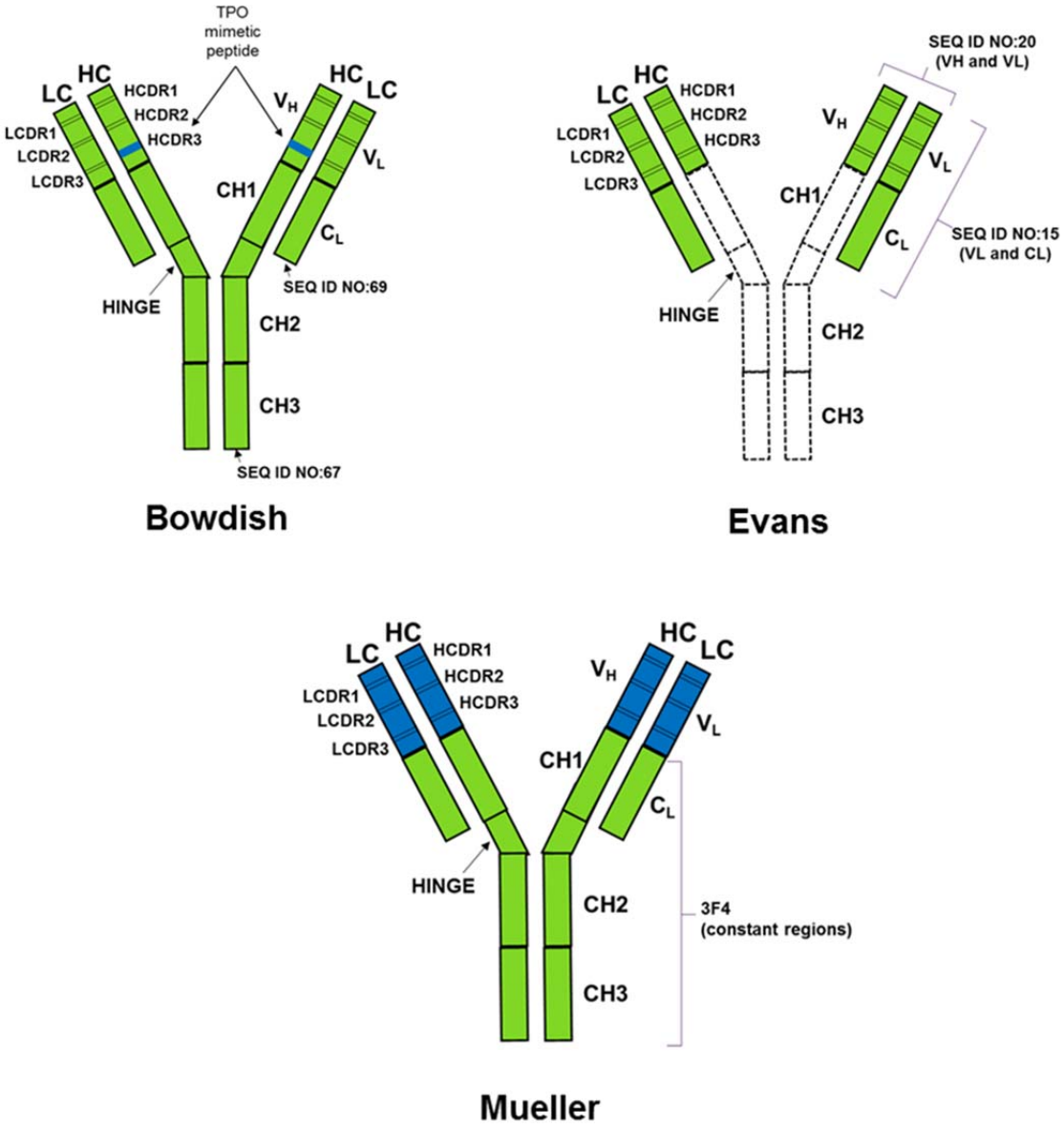

Figure 10.

[14] Green represents eculizumab sequences disclosed in the reference; blue represents non-eculizumab sequences in each reference. AMG1002, ¶60.

See AMG1002, ¶60.

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).

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 '504 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, ¶20. 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. 2005) (en banc); *see also*, 37 C.F.R. §42.100(b); 83 Fed. Reg. 51340, 51358 (Oct. 11, 2018).

"Immediate." Claim 9 recites that the claimed method "results in an *immediate* and sustained decrease in mean levels of lactate dehydrogenase (LDH)." AMG1001, claim 9. The '504 patent specification teaches "[t]he impact of terminal complement inhibition with eculizumab on chronic intravascular hemolysis in PNH patients was demonstrated in this study by an *immediate (one week)* and sustained decrease in mean levels of LDH." AMG1001, 22:22-25. Claim 10 depends from claim 9 and further requires that "the immediate decrease occurs *within one week* of administration of the antibody." AMG1001, claim 10. Thus, as Dr. Balthasar explains, a POSA would have understood the term "immediate" to include a decrease beginning "within one week" after administering the eculizumab. AMG1002, ¶¶64-65.

The meaning of all other claim terms in the '504 patent are plain on their

face and require no further construction. AMG1002, ¶65. 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)	1-3, 7-10	Hillmen
2	§103(a)	4-5	Hillmen and Bell
3	§103(a)	6	Hillmen, Bell, and Wang
4	§103(a)	1-5, 7-10	Bell, Bowdish, and Evans
5	§103(a)	6	Bell, Bowdish, Evans, and Wang
6	§103(a)	1-5, 7-10	Bell, Evans, and Mueller
7	§103(a)	6	Bell, Evans, Mueller, and Wang

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

- 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 B1 ("**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 '504 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) obvious over Hillmen, Thomas and Evans; and (iii) obvious over Hillmen, Thomas, Evans, and Wang. AMG1014, 557-561. Those rejections rested solely on disclosures in Thomas and Evans for eculizumab sequence information. *Id.* The examiner later allowed the '504 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, 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 region 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. 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 claims 1-3 and 7-10.

Hillmen anticipates claims 1-3 and 7-10. 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. Hillmen anticipates claim 1.

Dr. Balthasar confirms that Hillmen discloses all the limitations of claim 1, either expressly or inherently, and is enabling. AMG1002, ¶¶75-84.

1. Hillmen explicitly disclosed every element of claim 1, except for eculizumab's amino acid sequence.

Hillmen taught the claimed "method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH)" by disclosing "[e]leven transfusion-dependent *patients with PNH* received infusions of eculizumab…." AMG1004, Abstract. Hillmen also disclosed that "*eculizumab treatment* significantly reduced transfusion requirements, even though the levels of hemoglobin did not change significantly." *Id*, 558.

Hillmen also taught the claimed "administering to the patient a pharmaceutical composition comprising an antibody that binds C5" by disclosing administering pharmaceutical compositions of eculizumab (a known antibody that binds C5) to patients: "*patients* with PNH *received infusions of eculizumab*…." *Id*, Abstract. Hillmen further disclosed that "[t]his *antibody against terminal complement protein C5* reduces intravascular hemolysis, hemoglobinuria, and the need for transfusion…." *Id*, Abstract; *see also, id.*, 554 ("Patients *received infusions* of 600 mg *of eculizumab*….").

2. 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 SEQ ID NO:2 and SEQ ID NO:4, Hillmen inherently discloses the claimed sequences.

Despite admitting to the Office that the eculizumab disclosed in Hillmen necessarily comprised SEQ ID NO:2 and 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 [a patent] claims something 'new' over the disclosure of the [prior art]."). This precedent is squarely applicable here and compels finding anticipation. The '504 patent's mere claim to an amino acid sequence that Alexion admits was a property of a prior art compound (eculizumab) contributes nothing over the prior art.

3. Hillmen's disclosure is enabling.

Hillmen would have enabled a POSA to practice the method of claim 1 without undue experimentation. 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 practice the method of claim 1. AMG1002, ¶¶81-84.

The alleged invention and claims are directed to a method of treatment using eculizumab. This method was expressly taught by Hillmen. AMG1004, 553-554. And the general knowledge in the prior art was replete with disclosures, direction, and guidance of eculizumab's structure and amino acid sequence. AMG1002, ¶¶81-84.

Dr. Balthasar's Figure 10 above illustrates the art disclosing eculizumab amino acid sequences. *See* Section IV.E, *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, ¶82.

(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 regions of eculizumab. AMG1007, 44:4-13 (SEQ ID NO:20); AMG1008, 52-53, 58-61; AMG1002, ¶82.

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. AMG1002, ¶83

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. 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 methods were not new—Hillmen taught them. Alexion's admission that Hillmen's eculizumab inherently possesses the claimed sequences is binding under *Vitronics. Crish* dictates that Alexion cannot later claim the amino acid sequence it admits was inherent to an antibody in the prior art. And under *Donohue I* and *Donohue II*,

Hillmen is enabling.

B. Hillmen anticipates claim 2.

Claim 2 depends from claim 1, and further requires that the pharmaceutical composition be "administered by intravenous infusion." Claim 2 is anticipated because Hillmen expressly discloses that "[p]atients received infusions" of eculizumab. AMG1004, 554, Abstract. That Hillmen does not explicitly say "intravenous" is irrelevant. Other Alexion publications confirm that Hillmen administered eculizumab *via* intravenous infusion. *See* AMG1042 (2003), Abstract (disclosing that 11 PNH patients "completed a 3-month pilot study receiving 600 mg eculizumab by *intravenous infusion*…."); AMG1043 (2007), 4124 (disclosing Hillmen as administering eculizumab "via *intravenous infusion*" in the "12-week phase 2 pilot study."). AMG1002, ¶¶85-86.There can be no dispute that Hillmen's eculizumab "infusions" were intravenous. Indeed, the '504 patent itself refers to intravenous infusions of eculizumab as "infusions." *See e.g.,* AMG1001, 26:47 ("patients experienced headache within 48 hours of *infusion*").

Hillmen is enabling for the method of claim 2 for the same reasons provided for claim 1. AMG1002, ¶87. Moreover, preparing and administering pharmaceutical compositions by intravenous infusion was well within the routine skills of a POSA. *Id.*

C. Hillmen anticipates claim 3.

Claim 3 depends from claim 1 and further requires that "the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment." Hillmen anticipates claim 3 because Hillmen disclosed administering eculizumab dosages of 600 mg and 900 mg to adult men and women. AMG1004, Abstract, 554; AMG1002, ¶¶88-91.

As Dr. Balthasar explains, the amount of eculizumab in mg per kg administered to a patient will vary depending on the patient's body weight. AMG1002, ¶¶89-90. The FDA's Pharmacometrics Review in the Soliris® approval package provides the minimum and maximum patient body weights from 209 patients in six different eculizumab clinical trials, *including the Hillmen pilot study C02-001*, and definitively shows that Hillmen's 11 patients weighed between 48.5 kg and 157.2 kg. AMG1044, 8-9. Even with these lower and upper limits for body weight, the 11 patients treated in Hillmen necessarily received at least one dose of eculizumab of between 5 to 50 mg/kg:[15]

[15] According to the CDC, the average body weight for adult females and males in the U.S. is 74 kg and 87 kg, respectively. AMG1050, 61. Administering Hillmen's 600 and 900 mg doses of eculizumab to patients with these body weights would provide doses ranging from 6.9 to 12.2 mg/kg. AMG1002, ¶90.

Body weight (kg)	Dose (mg/kg) for 600 mg	Dose (mg/kg) for 900 mg
Minimum 48.5	12.4	18.6
Mean 85.4	7.0	10.5
Maximum 157.2	3.8	5.7

See AMG1044, 8-9; AMG1002, ¶89. Thus, Hillmen's disclosure of administering 600 mg or 900 mg eculizumab anticipates claim 3 because every patient in Hillmen's trial received at least one dose of eculizumab that would necessarily have fallen within the claimed range. AMG1004, 553; AMG1002, ¶¶89-90.

Hillmen is enabling for the method of claim 3 for the same reasons already discussed. AMG1004, 554; AMG1002, ¶91. Moreover, preparing and administering pharmaceutical compositions based on a patient's body weight (mg per kg) was well within the routine skills of a POSA. AMG1002, ¶91.

D. Hillmen anticipates claim 7.

Claim 7 depends from claim 1 and further requires that the "patient is anemic." Claim 7 is anticipated because Hillmen expressly discloses treating patients who had "received a diagnosis of aplastic *anemia*." AMG1004, 555. Hillmen is enabling for the method of claim 7 for the same reasons already discussed. AMG1002, ¶92.

E. Hillmen anticipates claim 8.

Claim 8 depends from claim 1 and further requires that the patient is dosed with "600 mg of the antibody via intravenous infusion every 7 ± 1 days for 4

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

Hillmen expressly taught this dosing regimen:

> Patients received 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.

AMG1004, 554; *see also*, AMG1002. ¶93. Hillmen is enabling for the method of claim 8 for the same reasons already discussed. AMG1002, ¶93.

F. Hillmen anticipates claim 9 and 10.

Claim 9 depends from claim 1 and further requires that "administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH)." Claim 10 depends from claim 9 and further requires that "the immediate decrease occurs within one week of administration of the antibody." Claims 9 and 10 are anticipated because Hillmen taught that administration of eculizumab resulted in an immediate and sustained decrease in LDH levels. AMG1004, Fig. 2.

Discussed above in Section VI, a POSA would have understood that "immediate" decrease includes a decrease beginning within one week after

administering the eculizumab. AMG1002, ¶65; AMG1001, 22:22-25. Hillmen disclosed that "[t]he decrease in lactate dehydrogenase began after a single dose of eculizumab in all patients" and that "[LDH] levels remained within or just above the normal range for the duration of the study." AMG1004, 555; AMG1002, ¶95. Dr. Balthasar confirms that Hillmen's data show an immediate and sustained decrease in LDH levels beginning within one week of administering eculizumab:

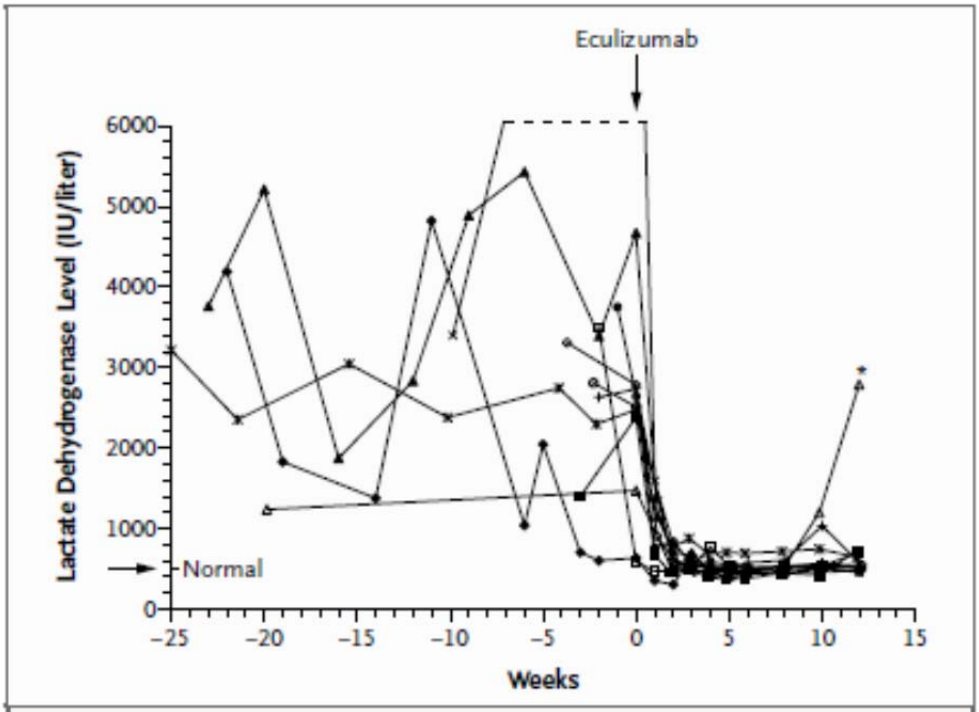

Figure 2. Analysis of Lactate Dehydrogenase Levels, a Biochemical Indicator of Hemolysis, in 11 Patients with Paroxysmal Nocturnal Hemoglobinuria up to 25 Weeks before and during 12 Weeks of Eculizumab Treatment.
The first dose of eculizumab is indicated by an arrow, as is the upper limit of the normal range of lactate dehydrogenase at the Leeds Teaching Hospital. The data point identified at week 12 by the asterisk represents a reading that was obtained from a duplicate serum sample since the original sample was lost. The dashed line represents off-scale points from one patient with a peak value of 12,100 IU per liter.

See AMG1004, Fig. 2; *see also*, AMG1002, ¶¶94-95.

Hillmen is enabling for the method of claims 9 and 10 for the same reasons already discussed. AMG1002, ¶95.

XI. Ground 2: claims 4-5 would have been obvious over Hillmen and Bell.

Hillmen taught all the elements of claim 1. While Hillmen might not explicitly disclose additional limitations of claims 4-5, those limitations were taught in Bell. A POSA would have had reason to combine Bell with Hillmen to arrive at claims 4-5, with a reasonable expectation of success. AMG1002, ¶¶97-109. And no objective indicia support patentability. *See* Section XIII.

Like Hillmen, Bell taught 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 (intravenous);

- dosing regimens;[16] and
- resulting data.

AMG1002, ¶¶39, 98; AMG1005, ¶¶[0081]-[0096].[17] Given the substantial overlap, a POSA would have had ample reason to combine Hillmen and Bell, with a reasonable expectation of success at achieving the claimed subject matter. No objective indicia of nonobviousness support patentability. *See* Section XIII.

Claim 4 depends from claim 1, and requires that "the pharmaceutical composition is in a *single unit dosage form*." Claim 5 depends from claim 4 and

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[16] 600 mg eculizumab weekly for four weeks, followed by a 900 mg dose, then 900 mg eculizumab every other week through week 12.

[17] 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 claims 1-4 and 7-10 for the same reasons discussed above for Hillmen. AMG1014, 767(¶6); *see also, id.*, 765 (study number "C02-001"); AMG1005, ¶[0082]; AMG1002, ¶120, n9. Hill '05, Hill '04, Hillmen '06, and Young '06 also anticipate claims 1-3 and 7-10 for the same reasons. AMG1014, 767(¶6), 765 (study numbers E02-001, X03-001, C04-001, and C04-002, respectively); AMG1047, 2559-2560; AMG1011, Abstract; AMG1012, 1235; AMG1013, Abstract.

requires that "the single unit dosage form is a *300 mg single unit dosage form*." AMG1001, 39:13-16. Bell taught these limitations, stating that eculizumab can be "administered in a variety of *unit dosage forms*. 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" unit dosage form as claimed. AMG1002, ¶¶102-103; 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, ¶103; AMG1046, 2989. Alexion agrees, telling the USPTO during prosecution[18] 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 unit dosage forms as claimed in claim 4 using routine

[18] U.S. Appl. No. 13/426,973 is the abandoned grandparent application of the '504 patent. AMG1001, face.

formulation preparation techniques that were standard and well-known in the art, particularly for intravenous therapeutic antibody formulations. AMG1002, ¶103. Indeed, the '504 patent mentions no "newly discovered" advantages of the single-unit-dosage-form claim limitation.

Moreover, a POSA would have arrived at the 300 mg strength (claim 5) through simple convenience and a logical application of knowledge in the art. AMG1002, ¶¶104-109. 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, ¶105.

To accommodate 600 mg and 900 mg dosages, a 300 mg single 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, ¶¶106-107. *See KSR*, 550 US at 416 ("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.") Alexion confirmed during a European opposition proceeding for a

related EP patent[19] that there is nothing critical about the claimed single unit 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 unit dosage form because doing so would have been a simple, conventional process of reconstitution and dilution. AMG1002, ¶108; AMG1053, ¶[0043]. 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, ¶108.

XII. Ground 3: claim 6 would have been obvious over Hillmen, Bell, and Wang.

Claim 6 depends from claim 1 and further requires formulating eculizumab as "a 300 mg single-use[20] formulation of 30 ml of a 10 mg/ml sterile, preservative

[19] EP Patent No. 2359834 is a European counterpart to the '504 patent.

[20] As explained above, a single unit dosage form is understood to be for a single use. AMG1002, ¶¶102-103; AMG1046, 2989. Alexion agrees. AMG1026, 208-209.

free solution." AMG1001, claim 6. The only added limitation in claim 6 over claim 5 is a "30 ml of a 10 mg/ml sterile, preservative free solution." This limitation would have been obvious over Hillmen, Bell, and Wang. AMG1002, ¶¶110-118. The teachings in Hillmen and Bell are discussed in Ground 2. Wang taught therapeutic antibody formulations, and explicitly taught formulating "*eculizumab* as the antibody therapeutic."[21] 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. AMG1002, ¶¶117.

First, 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]. Dr. Balthasar further explains that a POSA would also have generally known that therapeutic antibodies are routinely prepared in sterile, preservative-free solutions. AMG1002, ¶112. In fact, of 22 monoclonal

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[21] Wang's nebulization formulation is equally relevant to intravenous infusion because at bottom, Wang taught that liquid formulations of eculizumab at 1-30 mg/ml would be sufficiently stable and maintain its biological activity. AMG1028, ¶[0173]; AMG1002, ¶113.

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. *Id.*; AMG1056-AMG1076.

Second, Wang taught eculizumab formulations of between *1 and 30 mg/ml*, completely encompassing the claimed 10 mg/ml concentration. AMG1028, Fig. 10, ¶¶[0170]-[0172]; AMG1002, ¶113. "[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, ¶114; 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.[22] AMG1002, ¶115.

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. As discussed, 300 mg dosage units would be the easiest way to have one dosage form 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, ¶116.

Notably, the '504 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, ¶116.

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

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

sterile, preservative-free solution required mere conventional wisdom and routine skill. AMG1002, ¶117. And no objective indicia support patentability. *See* Section XIII.

XIII. Grounds 4-7: claims 1-10 would have been obvious over Bell and prior-art disclosures of anti-C5 antibody sequences.

Dr. Balthasar explains that a POSA reading Bell would have constructed a humanized 5G1.1 anti-C5 antibody, like eculizumab at least two different ways: (i) by combining the sequences taught in Bowdish and Evans **(Grounds 4-5)**; or (ii) by combining the sequences taught in Evans and Mueller **(Grounds 6-7)**. AMG1002, ¶¶119-209. And a POSA would have had reasons to combine these references with a reasonable expectation of success in arriving at the claimed subject matter. *Id.*. And no objective indicia support patentability. *See* Section XIII.

A. Ground 4: claims 1-5 and 7-10 would have been obvious over Bell, Bowdish, and Evans.

Discussed below, a POSA would have had a reason to combine Bell, Bowdish, and Evans with a reasonable expectation of successfully practicing the method of claims 1-5 and 7-10. AMG1002, ¶¶119-124.

1. Claim 1 would have been obvious.

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

Bell taught the claimed method of treating PNH by disclosing "a method of

treating a hemolytic disease such as, for example, *paroxysmal nocturnal hemoglobinuria ('PNH')*" and that "*[p]aroxysmal nocturnal hemoglobinuria ('PNH')* and other hemolytic diseases *are treated* in accordance with this disclosure." AMG1005, ¶¶[0003], [0012]; AMG1002, ¶¶125-129. Bell also taught the claimed treatment composition comprising an antibody that binds C5 by disclosing "an *anti-C5 antibody* selected from the group consisting of *h5G1.1-mAb (eculizumab)*…" suitable for treating PNH, and also that the antibody "h5G1.1-mAb" was "undergoing clinical trials under the tradename *eculizumab*." AMG1005, ¶¶[0012], [0052]. Bell further taught methods of preparing eculizumab compositions comprising "pharmaceutically effective carriers" and preparing "[f]ormulations suitable for injection." AMG1005, ¶¶ [0060], [0062]; AMG1002, ¶127.

Bell taught that eculizumab successfully treated patients suffering from PNH. AMG1005, ¶¶[0081]-[0096]; AMG1002, ¶128. Bell described an 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.[23] AMG1005, ¶[0082]. Bell concluded that "[p]atients in the two

[23] As already discussed, Bell's studies are identical to Hillmen, Hill '05, and Hill '04. *See* note 15, *supra*; *see also,* AMG1002, ¶39; AMG1014, 757, 765.

year study experienced a reduction in adverse symptoms associated with PNH." AMG1005, ¶[0096]. Thus, Bell would have motivated a POSA to practice the claimed method of treating PNH with an anti-C5 antibody like eculizumab. The only information arguably missing from Bell is the antibody amino acid sequences (SEQ ID NOs: 2 and 4 as claimed), but they were readily found in Bowdish and Evans.

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, ¶¶130-135. As explained in detail below, the missing HCDR3 sequence from Bowdish was taught by Evans. Dr. Balthasar's Figure 11 below depicts this combination of art providing the complete eculizumab sequence:

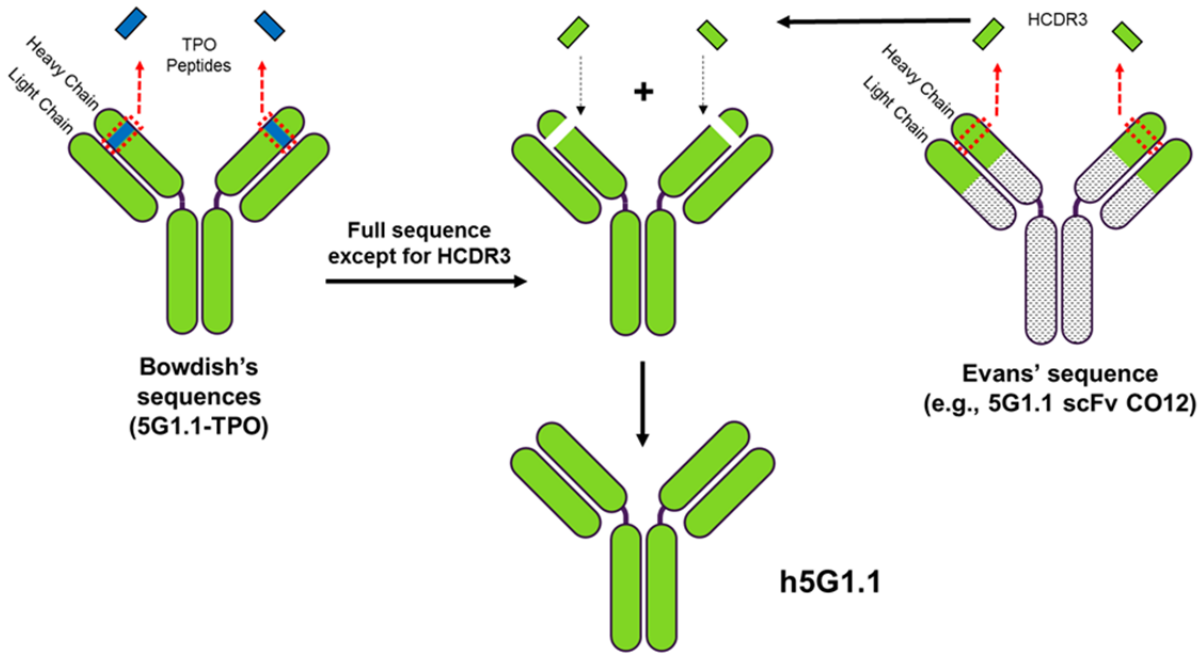

Figure 11.

AMG1002, ¶120.

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, ¶¶130-133. 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::

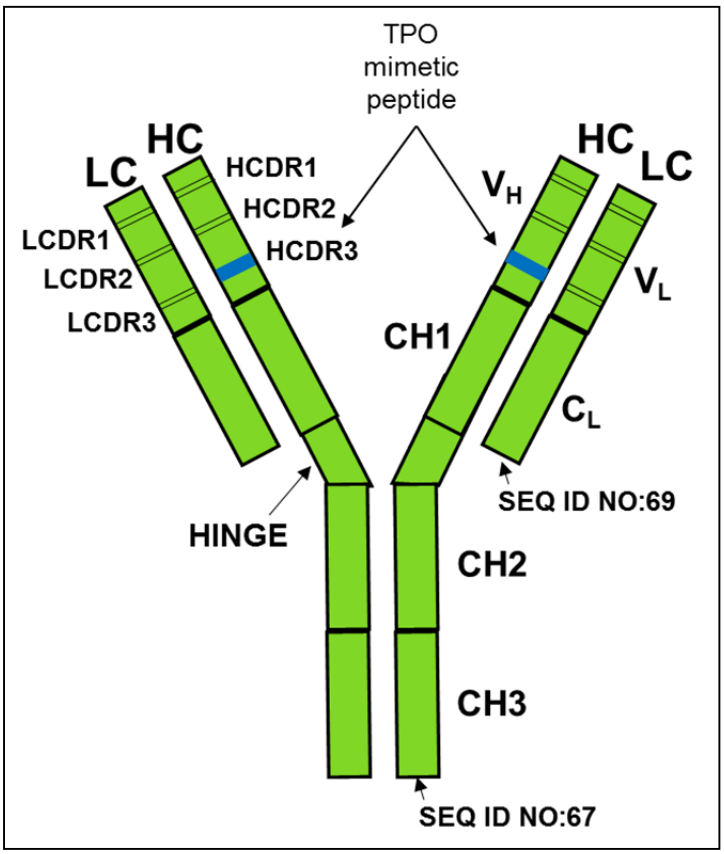

Figure 3.

AMG1002, ¶¶51-53; 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, ¶¶133-138.

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, ¶133. Thus, the POSA would have known that the leader sequences in Bowdish's Figures 13A-13B are not part of the mature antibody sequence[24]. AMG1006, Figures 13A-13B; AMG1002, ¶133; 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, ¶¶137. The missing HCDR3 sequence, however, was taught in Evans, and Bowdish expressly directed a POSA to Evans. AMG1006, ¶[0191].

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[24] 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…." AMG1014, 513; *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, ¶136. 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, ¶136. 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, ¶136. Dr. Balthasar's Figure 11 above shows this, where Evans' HCDR3 sequence is extracted and inserted into Bowdish's construct. AMG1002, ¶120.[25] 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, ¶¶137-138. Dr. Balthasar confirms by sequence alignment that this combination provides a sequence identical to the '504

[25] 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, ¶121.

patent's SEQ ID NO: 2. *Id.*.

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 safe and effective for treating PNH patients. AMG1005, ¶¶[0083]-[0096]. Because Bell does not expressly provide the amino acid sequence of its antibody, a POSA would have looked to other teachings in the art, like Bowdish and Evans. AMG1002, ¶¶139-142.

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, ¶¶43-45; 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, ¶140. 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, ¶141.

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, ¶142. For example, Bell stated: "[m]ethods for the preparation of *h5G1.1-mAb* [eculizumab] … are described in [Evans][26] … incorporated herein in [its] entirety …." AMG1005, ¶[0052]. And Bowdish similarly stated: "[c]onstruction of *5G1.1* is described in [Evans], incorporated herein by reference."[27] 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 peptide sequence in Bowdish's antibody with the HCDR3 sequence from Evans—

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[26] 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, ¶48; *see also*, Section IV.D, *supra.*

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

to yield predictable results: a 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 comprises a heavy chain consisting of SEQ ID NO:2 and a light chain consisting of SEQ ID NO:4 as claimed. AMG1002, ¶¶52-53, 137-138.

A POSA would have reasonably expected to successfully perform the method of claim 1 because (i) making a humanized anti-C5 antibody would have required only basic molecular biology techniques to substitute Evans' HCDR3 sequence for Bowdish's TPO-mimetic peptide sequence; (ii) antibody production methods were well-known in the art (see, e.g., AMG1006, ¶¶[0130]-[0131]); and (iii) Bell taught that a humanized anti-C5 antibody was a safe and effective treatment for PNH, and provided methods and guidance on how to administer the treatment (AMG1005, ¶¶[0081]-[0096]). AMG1002, ¶¶143-144). This expectation is bolstered by numerous publications of successful clinical trials involving treating PNH with the humanized anti-C5 antibody, eculizumab. *See, e.g.,* AMG1004; AMG1042; AMG1047; AMG1011; AMG1005; AMG1012; AMG1013; AMG1002, ¶143.

2. Claims 2-5 and 7-10 would have been obvious.

Claims 2-10 all depend directly or indirectly from claim 1. All of the above arguments above regarding claim 1 also apply to these dependent claims.

a) Claim 2: intravenous infusion.

Bell and Evans both taught "intravenous infusion." Bell taught that eculizumab can be administered "via *intravenous infusion* by injection" and included a working example in which patients "received a weekly 600 mg *intravenous infusion* of anti-C5 antibody." AMG1005, ¶¶[0060], [0082]. Evans discloses that "[a]dministration of the anti-C5 antibodies will generally be performed by an intravascular route, e.g., via *intravenous infusion* by injection." AMG1007, 18:29-31; *see also, id.,* 142:53-59, 143:5-8.

A POSA would have administered the eculizumab composition intravenously because (i) both Bell and Evans expressly taught this route and (ii) intravenous infusion was standard for therapeutic antibodies. AMG1002, ¶¶145-146. And a POSA would have had a reasonable expectation of success because Bell described successful results using this method. AMG1005, ¶¶[0081]-[0096]; AMG1002, ¶146.

b) Claim 3: dosage level of between 5 mg/kg and 50 mg/kg.

Evans taught claim 3's dosage: "[d]osage levels of the antibodies for human subjects are … preferably between about *5 mg per kg and about 50 mg per kg per*

patient per treatment." AMG1007, 18:7-11. Moreover, as explained above in the anticipation analysis for claim 3, administering 600 mg or 900 mg eculizumab to adult men and women—as taught in Bell—results in patients receiving doses within claim 3's dosage range. *See* Section IX.C, *supra*; AMG1005, ¶[0082]; AMG1002, ¶¶89-90, 148.

A POSA would have administered eculizumab at a dosage level of between 5 mg/kg and 50 mg/kg per patient per treatment with a reasonable expectation of success because Evans expressly taught this dosing range and Bell taught that doses within this range could successfully treat PNH. AMG1007, 18:7-11; AMG1005, ¶¶[0081]-[0096]; AMG1002, ¶¶147-149.

c) Claim 8: dosing regimen.

Bell disclosed a regimen claimed in claim 8, treating PNH patients with "a weekly 600 mg intravenous infusion" of eculizumab for four weeks, followed by "900 mg of eculizumab 1 week later then 900 mg on a bi-weekly basis." AMG1005, ¶[0082]. Bell also taught that this treatment regimen was effective for treating PNH patients. AMG1005, ¶¶[0081]-[0096].

Thus, Bell disclosed a regimen having all of the limitations of claim 8 and would have provided a POSA with a reason to administer a humanized anti-C5 antibody as taught, with a reasonable expectation of success as discussed above. AMG1002, ¶¶150-152.

d) Claims 4 and 5: single unit dosage forms.

As discussed in Ground 2, Bell taught that eculizumab can be "administered in a variety of *unit dosage forms*." AMG1005, ¶[0058]; AMG1002, ¶¶153-154. Evans provided the same teaching *verbatim*. AMG1007, 17:60-61.

A POSA would have understood that a "unit dosage form" of an antibody as taught in Bell and Evans is formulated for use in a single patient and is therefore a "single" unit dosage form as claimed. AMG1002, ¶154; AMG1046, 2989; AMG1051, 1. A POSA reading Bell and Evans would have therefore prepared the a humanized anti-C5 antibody formulation as a single unit dosage form using routine formulation preparation. Single unit dosage forms were routinely used for intravenous therapeutic antibody formulations. AMG1002, ¶154.

Also discussed above, a POSA would have arrived at a single unit dosage form of 300 mg as claimed in claim 5 through simple convenience and logic. AMG1002, ¶158. A POSA would have had incentive to design a 300 mg single unit dosage amount as claimed because 300 mg would have been the most obvious and convenient means for administering the 600 mg and 900 mg doses taught by Bell. AMG1002, ¶¶156-158. And Alexion admits there is nothing critical about the claimed single unit dosage. AMG1027, 1104(¶5.3.9).

A POSA reading Bell and Evans would have had a reasonable expectation of successfully preparing a 300 mg single unit dosage form for the same reasons

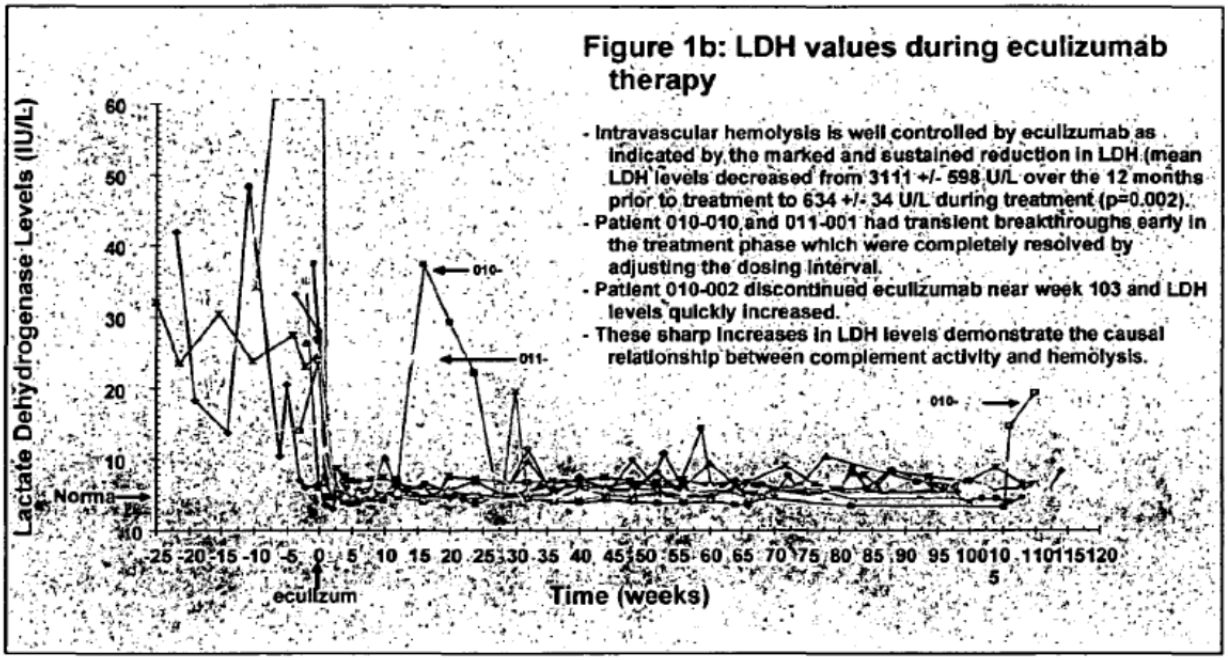
discussed above in Ground 2. AMG1002, ¶¶155, 159; *see* Section X.

e) Claim 7: patient is anemic.

Bell taught that, by administering eculizumab to a patient suffering from PNH, "the effects of PNH and other hemolytic diseases (including symptoms *such as … anemia*…) are eliminated or decreased." AMG1005, ¶[0037]; *see also*, *id.*, ¶¶[0014], [0066], [0076]-[0077]. Thus, Bell would have given the POSA a reason to administer a humanized anti-C5 antibody to a PNH patient that is anemic, with a reasonable expectation of success, because Bell expressly taught this method and showed successful results of treating PNH patients. AMG1005, ¶¶[0081]-[0096]; AMG1002, ¶¶160-161.

f) Claims 9 and 10: immediate decrease in LDH levels

Bell taught the clinical outcomes required by claims 9 and 10. AMG1002, ¶¶162-164; AMG1005, FIG. 1B. Bell taught that "[t]he *LDH levels were decreased* by greater than 80% as compared to pre-treatment levels." AMG1005, ¶[0085]. And as Dr. Balthasar explains, Bell's data show an immediate decrease in LDH beginning within one week of administering eculizumab, followed by a sustained decrease:



AMG1005, FIG. 1b; AMG1002, ¶164. Bell described the data in Fig. 1b as showing a "*marked and sustained reduction* in LDH (*mean LDH levels decreased*…)." *Id.; see also,* AMG1005, ¶[0085].

A POSA would have understood that Bell's decrease in mean LDH levels is an "immediate decrease" because Bell shows a decrease in LDH levels beginning within one week of administration of eculizumab administration. AMG1005, FIG. 1B; AMG1002, ¶164. A POSA also would have understood that this decrease is "sustained" because Bell shows the LDH levels remaining decreased throughout two years (105 weeks) of treatment. *Id.*

A POSA reading Bell, therefore, would have had reason to administer a humanized anti-C5 antibody to a patient to reduce the mean LDH levels with a

reasonable expectation of success because Bell taught (i) that "LDH levels are used as an objective indicator of hemolysis" – i.e., reduced LDH levels are clinically beneficial in PNH patients; and (ii) that administering eculizumab caused an immediate and sustained decrease in LDH levels. AMG1005, ¶[0085], FIG. 1B; AMG1002, ¶165.

B. Ground 5: claim 6 would have been obvious over Bell, Bowdish, Evans, and Wang.

As discussed in Ground 3, claim 6 would have been obvious over Hillmen, Bell, and Wang. *See* Section XI. Claim 6 also would have been obvious over Bell, Bowdish, Evans, and Wang for the same reasons, namely:

(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, ¶¶167-168. And a POSA would have known that therapeutic antibodies are routinely prepared in sterile, preservative-free solutions. AMG1002, ¶¶167-168; 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, ¶168.

(iii) A POSA would have prepared the a humanized anti-C5 antibody formulation in 30 ml single-use dosage forms using simple mathematics based on a 300 mg dosage unit concentrated at 10 mg/ml. AMG1002, ¶168. 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, ¶168. A POSA reading Bell, Bowdish, Evans, and Wang would have had a reasonable expectation of successfully practicing the method of claim 6 for the same reasons discussed above in Ground 3. AMG1002, ¶¶169-170; *see* Section XI. And no objective indicia support patentability. *See* Section XIII.

C. Ground 6: claims 1-5 and 7-10 would have been obvious over Bell, Evans, and Mueller.

Claims 1-5 and 7-10 also would have been obvious in view of Bell, Evans, and Mueller. AMG1002, ¶¶171-205. Discussed below, a POSA would have had a reason to combine these references with a reasonable expectation of successfully practicing the claimed method. And no objective indicia support patentability. *See* Section XIII.

1. Claims 1-5 and 7-10 would have been obvious over Bell, Evans, and Mueller.

Discussed below, a POSA would have had a reason to combine Bell, Evans, and Mueller with a reasonable expectation of successfully practicing the method of claims 1-5 and 7-10. And no objective indicia weigh in favor of patentability. *See* Section XIII.

a) Claim 1 would have been obvious.

(1) Bell expressly taught all the limitations of claim 1 except the eculizumab amino acid sequences

Bell's teachings discussed in Grounds 2 and 3 also apply in Ground 4. As already discussed, the only element of claim 1 not expressly taught in Bell is that its humanized anti-C5 antibody "comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." This information was, however, taught in Evans and Mueller. AMG1002, ¶¶171-176.

(2) 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, ¶¶172-173, 183-185. 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, ¶¶172-173, 186. Dr. Balthasar's Figure 14 below depicts this combination of art

providing the complete eculizumab sequence:

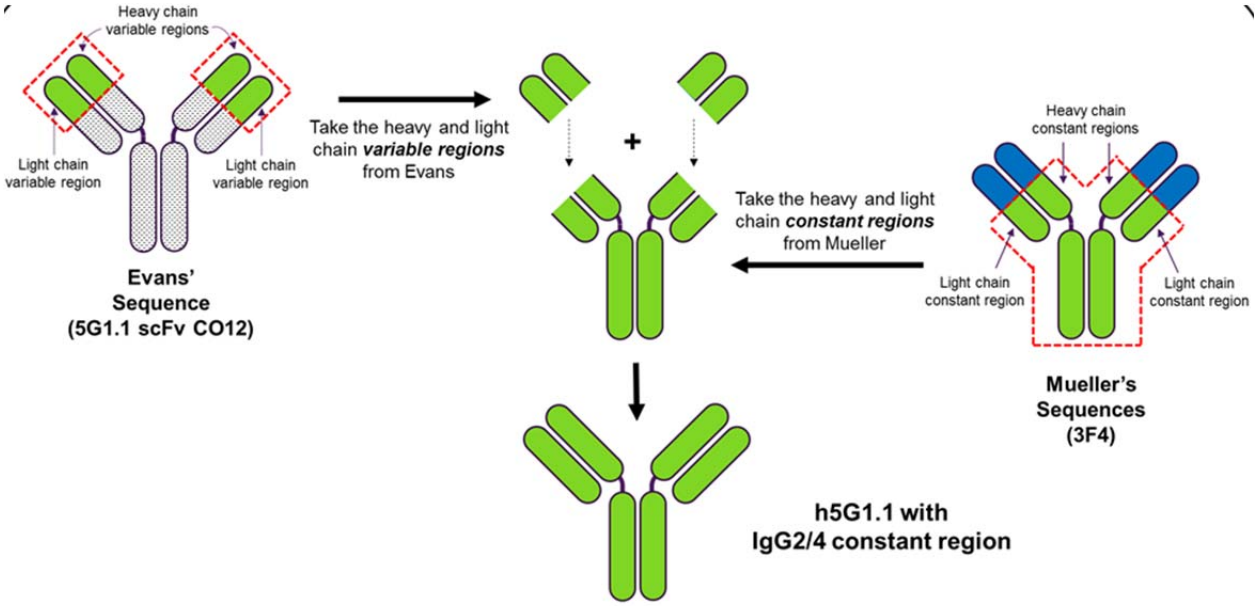


Figure 14.

See AMG1002, ¶173.

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, ¶¶183-184. 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[28] along with their

[28] A POSA would have known that a scFv comprises light and heavy chain

amino acid sequences. *Id.* (constructs 2 and 11-18); AMG1002, ¶¶178, 185. 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 that 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. 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 IgG2/IgG4 constant region ("HuG2/G4"). AMG1008, 12:37, FIG. 15; AMG1005, ¶[0052]; AMG1034, 1279; AMG1049, 838-839; AMG1002, ¶190.

As Dr. Balthasar explains, Mueller disclosed the amino acid sequence of a

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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, ¶178.

hybrid IgG2/IgG4 heavy chain constant region when Mueller disclosed the sequence of the chimeric anti-VCAM "3F4" antibody. AMG1002, ¶186; 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, ¶186; 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, ¶186. 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, ¶186.

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, ¶186. 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, ¶179.

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, ¶¶56-57, 179. 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. *Id.*; 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. 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, ¶¶180-182. This is shown in Dr. Balthasar's Figure 14 above, where the green portions depict Evans' heavy and light chain variable regions. AMG1002, ¶173; 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, ¶184; 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, ¶185. 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, ¶185.

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, ¶185; 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, ¶185.

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.[29] *See* Dr. Balthasar's Figure 14 above; AMG1002, ¶¶186-188.

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, ¶¶187-188.

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

Again, a POSA would have 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, ¶¶189-190. A POSA reading Bell 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, ¶¶189-190. A POSA would have also looked to Mueller because Mueller disclosed an h5G1.1 antibody named "h5G1.1 CO12 HuG2/G4

[29] 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, ¶121.

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, ¶190.

Evans and Mueller taught complementary, familiar elements of eculizumab's amino acid sequences. AMG1002, ¶¶191-192. 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, ¶192.

A POSA would have had a reasonable expectation of successfully practicing the method of claim 1 because (i) making a humanized anti-C5 antibody would have required only basic molecular biology techniques to combine Evans' scFv variable regions with Mueller's constant regions; (ii) antibody production methods already were well-known (see, e.g., AMG1006, ¶¶[0130]-[0131]); and (iii) Bell

taught that a humanized anti-C5 antibody was a safe and effective treatment for PNH, and provided methods and guidance on how to administer the treatment (AMG1005, ¶¶[0081]-[0096]). AMG1002, ¶192. This expectation is bolstered by numerous publications of successful clinical trials involving treating PNH with eculizumab. *See, e.g.,* AMG1004; AMG1042; AMG1047; AMG1011; AMG1005; AMG1012; AMG1013.

b) Claims 2-5 and 7-10 would have been obvious.

The additional elements required in claims 2-5 and 7-10 in Ground 6 are disclosed in Bell and Evans (and general knowledge in the art). Those same disclosures and arguments are presented above in Ground 4. Therefore, the rationales and conclusions presented in Ground 4 for claims 2-5 and 7-10 also apply to Ground 6 for the same reasons. AMG1002, ¶¶193-205.

D. Ground 7: claim 6 would have been obvious over Bell, Evans, Mueller, and Wang.

The additional elements required in claim 6 in Ground 7 are disclosed in Wang (and general knowledge in the art). Those same disclosures and arguments are presented above in Grounds 3 and 5. Therefore, the rationales and conclusions presented in Grounds 3 and 5 for claim 6 also apply to Ground 7 for the same reasons. AMG1002, ¶¶206-209.

XIV. 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 that "the non-natural, protein-engineered, heavy chain of eculizumab" (i.e., the hybrid IgG2/IgG4 constant region) 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 region 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, ¶¶210-212. 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, ¶212. 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 is not a *novel feature* of the claims. Discussed above, numerous therapeutic antibodies were formulated at this concentration, *including eculizumab*. AMG1002, ¶¶113-114; 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, ¶¶213-214.

Petitioner is not aware of any other alleged objective indicia, and reserves the right to rebut any evidence Alexion asserts. *Amneal Pharms., LLC v. Supernus Pharms., Inc*., IPR2013-00368, Paper 8, at 12-13 (Dec. 17, 2013); AMG1002, ¶215.

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 the '504 patent is available for IPR and Amgen is not barred or estopped from requesting IPR of any '504 patent 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 9,732,149 (IPR2019-00741), which are related to the '504 patent and also owned by Alexion.

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

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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 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. 9,725,504 contains 13,974 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. 9,725,504" 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. 9,725,504:

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