UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

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Case No. IPR2019-00741
Patent: 9,732,149

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PATENT OWNER RESPONSE PURSUANT TO 37 C.F.R. § 42.120

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I. INTRODUCTION

Claim 1 of the U.S. Patent No. 9,732,149 ("the '149 patent") recites the novel, uniquely-engineered amino acid sequence of SOLIRIS®, the groundbreaking, commercially successful anti-C5 monoclonal antibody developed by Alexion. SOLIRIS®, also referred to today by its non-proprietary name "eculizumab," is a first-in-class treatment for patients with the rare, potentially fatal blood disease paroxysmal nocturnal hemoglobinuria ("PNH"), caused by red blood cells losing their normal protection against the "complement" immune pathway. SOLIRIS® works by binding to component 5 ("C5") of the complement pathway and preventing its cleavage into components "C5a" and "C5b," which mediate downstream effects of the complement pathway, including hemolysis in patients with PNH.

Prior to March 15, 2007, the priority date of the '149 patent, the unique amino acid sequence of SOLIRIS® recited in claim 1 of the '149 patent was ***not*** publicly known or disclosed in the prior art. While a person of ordinary skill in the art ("POSA") as of that date would have known that Alexion had designed and clinically tested an antibody named "eculizumab," the POSA would not have known that "eculizumab" had the uniquely-engineered amino acid sequence claimed in the '149 patent. That is because the literature as of March 15, 2007 consistently identified "eculizumab" as the antibody described in the "Thomas"

publication (AMG1023), which has a naturally-occurring "***IgG4***" heavy chain constant region. In contrast, the novel antibody of the '149 patent has a very different, uniquely-engineered, non-naturally occurring constant region. A POSA would not have known of any antibody with the specific sequence recited in claim 1 of the '149 patent, and would have had no basis to reasonably expect that such an antibody would bind C5 or have the therapeutic utility that the literature on "eculizumab" attributed to Thomas's IgG4 antibody.

Amgen has not shown how any of the prior art of its Grounds disclosed or would have led a POSA to the uniquely-engineered amino acid sequence of SOLIRIS® recited in claim 1 of the '149 patent. Instead, Amgen disregards the perspective of a POSA as of March 15, 2007, and impermissibly uses its ***hindsight knowledge*** of the '149 patent's novel, previously-undisclosed claimed sequence to misstate the disclosures of the prior art, pick and choose from those misstated disclosures, and reconstruct the claimed invention using the '149 patent's teachings as a guide. When the art is viewed from the proper perspective of a POSA, each of Amgen's Grounds fails.

Amgen's Grounds 1 and 2 fail because Amgen incorrectly presumes that a POSA would have understood that the clinical publications Hillmen (AMG1004) and Hill (AMG1047) somehow disclosed the claimed sequence of the '149 patent by using the name "eculizumab." But nothing within the four corners of the

Hillmen and Hill publications disclosed the present-day knowledge that eculizumab has the uniquely-engineered amino acid sequence described and claimed in the ’149 patent. Rather, as the Board correctly recognized, both Hillmen and Hill identified “eculizumab” as the ***IgG4 antibody of Thomas***. (*See, e.g.*, Paper No. 15, 20-21 & n.14, 24-25, 27.)

Amgen’s Ground 3, styled as anticipation by Bowdish (AMG1006), fails because a POSA would not have seen ***any*** disclosure in Bowdish of the uniquely-engineered C5-binding antibody consisting of SEQ ID NOs: 2 and 4 claimed in the ’149 patent. Bowdish disclosed neither “eculizumab” nor any other antibody that binds C5. Rather, Bowdish described a very different compound – a “peptide-mimetic” compound designed solely for presenting the peptide hormone “TPO” on a neutral “scaffold” to enhance the peptide’s stability and half-life.

Recognizing Bowdish’s deficiencies, Amgen’s Ground 3 instead culls and recombines sequences from ***two*** documents: Bowdish, and Evans (AMG1007) – a patent that did not describe ***any*** full-length humanized antibodies for binding C5, let alone the antibody of the ’149 patent. Ground 3 first fails for lack of proof, because Amgen and its declarant admittedly neglected to consider and introduce in the record the ***actual*** document that Bowdish cites – the “’283 application,” which is ***not*** AMG1007, the Evans patent itself. Even using the Evans patent as a stand-in for the ’283 application (which it is not), Amgen overreads Bowdish’s single

reference to Evans for "[c]onstruction of 5G1.1" – a mouse antibody whose sequence is nowhere close to the uniquely-engineered humanized antibody claimed in the '149 patent. Amgen cannot rewrite Bowdish's limited reference to construction of Evans's "5G1.1" mouse antibody as an open-ended incorporation of Evans's entire 93-page disclosure, including sequences for humanized fragments that are ***not*** the "5G1.1" antibody.

Even if Amgen were correct to read Bowdish as incorporating Evans in its entirety (which it does not) Amgen still cannot show how Bowdish anticipates the '149 patent, when the presently claimed antibody is not disclosed ***anywhere*** in the two references, alone or combined. Instead, Amgen attempts to recreate the '149 patent's novel, unique claimed sequence by mixing and matching bits and pieces of sequences plucked from Bowdish's full-length TPO-mimetic compound, and structurally distinct "scFv" compounds from Evans. That cannot be anticipation, which requires that "the prior art reference...show[s] the claimed invention ***arranged or combined in the same way*** as recited in the claim." *Net MoneyIN v. Verasign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008).[1]

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[1] Unless otherwise noted, all emphasis is added, and all internal citations and internal quotation marks are omitted.

Amgen's Grounds 4 and 5, alleging obviousness, fail because they rely on post-hoc knowledge of the '149 patent's unique claimed sequence to reconstruct that invention from bits and pieces of structurally and functionally distinct compounds in unrelated art. *See Merck Sharpe & Dohme B.V. v. Warner Chilcott Co.*, 711 Fed. App'x 633, 637 (Fed. Cir. 2017) ("[U]sing the [patent-in-suit] as a roadmap to piece together various elements of [the prior art] . . . represents an improper reliance on hindsight."). As Dr. Balthasar conceded at deposition, he was handed his cited prior art by counsel; he read only the portions of his references that he contends showed obviousness of the claimed invention; he could not testify with any "confidence" as to whether his references did or did not disclose key aspects of the claimed invention; and he assembled his figures based on the claimed sequence of the '149 patent that was not available to a POSA prior to March 15, 2007. (ALXN2032, 64:23-65:14, 74:16-75:5, 77:7-78:2, 85:10-17, 108:17-109:10, 148:24-149:10, 180:8-11, 244:17-245:9, 267:17-268:11.)

For example, Amgen's Ground 4 contends that a POSA would have started with Bell (AMG1005) – which identified "eculizumab" as a clinically studied anti-C5 antibody – and then surmises that a POSA would have turned to Bowdish and Evans for the sequence of "eculizumab." But as the Board recognized, Bell – like Hillmen, Hill, and the other pertinent art – informed a POSA as of March 15, 2007 that "eculizumab" was Thomas's ***IgG4*** antibody. (Paper No. 15, 21 n.14.)

Amgen cannot explain why a POSA would have ignored the clear and unequivocal direction toward Thomas' IgG4 antibody and instead looked to Bowdish, which was not even cited by Bell.

Nothing in Bowdish or Evans remotely indicated to a POSA that either reference, alone or in combination, disclosed the specific full-length antibody "eculizumab." A POSA would have had no reason to jump from Bell to the combination of Bowdish and Evans to learn anything about the structure or sequence of "eculizumab." It is undisputed that Evans did not disclose ***any*** full-length humanized antibody, let alone "eculizumab."

Likewise, nothing would have guided a POSA to turn from Bell to Bowdish for the structure of "eculizumab." Amgen assumes that a POSA considering the structure and sequence of Bell's "eculizumab" would have (1) selected Bowdish, rather than Thomas, as a starting point – despite that Bowdish never mentions "eculizumab," is not cited by Bell or any other prior art references defining "eculizumab," and does not even contain any C5-binding or clinical data suggesting that it might be associated with "eculizumab"; (2) identified Bowdish's TPO-mimetic compound as relating to a humanized antibody with a hybrid IgG2/IgG4 constant region – even though nothing in Bowdish contains such a statement; and (3) associated the purported IgG2/IgG4 structure of Bowdish's TPO-mimetic compound with "eculizumab" – despite the teaching in Bell itself,

and the consistent teaching throughout the prior art, that a POSA would have understood "eculizumab" to be an ***IgG4*** isotype antibody, which would not match with the sequence of a hybrid IgG2/IgG4 antibody.

Amgen's Ground 5 uses improper hindsight to recreate the claimed sequence of the '149 patent from sequences plucked from Mueller (AMG1008) and Evans. Mueller concerned antibodies directed at "VCAM" – a very different target from C5 – and used the antibody "h5G1.1 CO12 HuG2/G4 mAb" only as an "isotype control" for experiments involving VCAM. As the Board noted, Mueller identified only an ***IgG4*** isotype antibody (*i.e.*, the isotype of Thomas) as an "anti-C5 antibody," and taught nothing about the C5 binding or clinical properties of "h5G1.1 CO12 HuG2/G4 mAb."

Nor would a POSA would have been motivated to combine the sequences in Evans and Mueller – neither of which cites to the other – in the exact manner to get the specific claimed antibody sequence of the '149 patent. As the Board correctly recognized, nothing in Evans or Mueller instructs whether or how such a combination should be done, including "precisely the portions of Evans's and Mueller's disclosed amino acid sequences to use and which to discard so as to arrive at a final antibody that perfectly matched the claimed antibody." (Paper No. 15, 53-54.)

II. BACKGROUND

A. Design of Humanized Monoclonal Antibodies for Human Therapeutic Use Was a Complex, Unpredictable Art

There is no dispute that as of March 15, 2007, a POSA would have understood a "monoclonal" antibody (including a "humanized monoclonal antibody" such as "eculizumab") to be a single, unique antibody with one defined structure, and critically, ***one unique primary amino acid sequence*** for the entire antibody. (ALXN2022, ¶70; ALXN2032, 10:9-22, 11:10-17.) A humanized monoclonal antibody, in turn, was understood to be a unique antibody with a unique sequence, designed by grafting mouse monoclonal antibody sequences associated with antigen binding into a human monoclonal antibody. (ALXN2022, ¶¶76, 78.) And a POSA would have understood that a humanized monoclonal antibody for therapeutic use – the subject matter of the invention described and claimed in the '149 patent – was a humanized monoclonal antibody intended to bind its target and achieve a desired biological and therapeutic activity when administered to patients, while maintaining sufficient safety to be suitable for human administration. (*See* ALXN2022, ¶¶76-82, 86-90; ALXN2032, 43:15-22, 46:20-48:2.)

Critically, a POSA would have understood that development of a "humanized" antibody intended for human therapeutic use was a complex and

unpredictable art. (ALXN2022, ¶¶76-90.) A particular new humanized monoclonal antibody could not simply be assumed to retain the original mouse antibody's binding affinity and biological activity against its target antigen. Accordingly, a new humanized monoclonal antibody would need to be tested *in vitro* to establish its binding properties and its biological activity. (ALXN2022, ¶82.) Further, to determine the suitability of a new humanized antibody as a therapeutic agent, additional extensive testing would need to be performed, including "pre-clinical" toxicology testing in animal species; clinical testing of efficacy, immunogenicity, and overall safety; and pharmaceutical formulation work to confirm that a suitably stable composition could be safely and efficaciously administered to people. (ALXN2022, ¶¶77-90; ALXN2032, 46:20-48:2.)

Further, a POSA as March 15, 2007 could not reasonably extrapolate the *in vitro* or clinical properties of one monoclonal antibody with a unique amino acid sequence to a different antibody with a different sequence. A POSA would have understood that antibodies were complex three-dimensional structures, and that a monoclonal antibody's specific amino acid sequence was essential to its structure and function. (ALXN2022, ¶¶62-63, 70, 116.) In particular, it was known that even small changes in an antibody's sequence could affect its critical properties. (ALXN2022, ¶¶104-117.)

For example, a POSA would have understood that sequences ***beyond*** a monoclonal antibody's "CDRs" could substantially influence its antigen-binding properties, including its "affinity" (tightness of binding) for the target antigen, "specificity" for binding the target antigen versus non-targets, and "fine specificity" for binding the target antigen in the particular region ("epitope") needed to provide the desired therapeutic activity. (ALXN2022, ¶¶104-117.) It was well-known that non-CDR amino acids within an antibody's "variable" region (*i.e.*, "framework" residues) could impact antigen binding, either by direct involvement in binding or indirect effects on three-dimensional antibody structure. (ALXN2022, ¶106.) A POSA also would have known that the ***constant regions*** of monoclonal antibodies play an indirect role in antigen binding, and that switching between different constant regions ("isotype switching") could significantly impact antigen binding, even while leaving the variable region unchanged. (ALXN2022, ¶107-114.) In particular, the art described how changes to the "CH1" and "hinge" portions of the heavy chain constant region impact antigen affinity and specificity. (ALXN2022, ¶113; ALXN2012, 3388, 3391-92; ALXN2009, 13917-18, 13924.)

Once a suitable humanized monoclonal antibody was designed and tested to show it has its desired *in vitro* activity, it would need to be further studied with clinical tests in humans. (ALXN2022, ¶¶86-88.) A POSA would have been particularly concerned about the unpredictability of a humanized monoclonal

antibody for therapeutic use if, in addition to the mouse sequences of the variable region, it contained a non-naturally occurring constant region that was not known to have been clinically tested and shown to be suitable for human administration (*e.g.*, a hybrid constant region fusing sequences from different isotypes). (ALXN2022, ¶86.)

A POSA would have also understood that truncated antibody-like molecules could be made, containing amino acid sequences that include less than a full-length, intact humanized monoclonal antibody. (ALXN2022, ¶¶91-93.) While commonly called "fragments," these compounds were typically made by recombinant DNA means, rather than "broken off" from a full-length, pre-existing antibody. (ALXN2022, ¶91; ALXN2032, 143:18-22.) For example, a humanized single-chain Fv or "scFv" compound could be made, containing only the variable light and heavy chain regions connected by a linker; or an "Fab" compound could be made, containing a complete light chain but only the variable and CH1 constant region of the heavy chain ("Fd"), with no intact "Fc" region (the stem of the Y-shaped antibody structure). (ALXN2022, ¶¶67, 92; ALXN2032, 143:8-25.) A POSA would have understood that these "fragments" were very different from a full-length humanized antibody, and have different properties (*e.g.*, shorter half-life but greater tissue penetration). (ALXN2022, ¶93.) A POSA would have further understood that because the constant regions of a full-length, intact antibody could

impact its antigen-binding properties as well as its immunogenicity, the properties of a "fragment" lacking a full heavy chain constant region could not reliably be extrapolated to a new, untested full-length humanized monoclonal antibody. (ALXN2022, ¶¶93, 105-117.)

B. Naming of Humanized Monoclonal Antibodies

A POSA as of March 15, 2007 would have understood that different naming conventions were used for humanized monoclonal antibodies at different stages of development. (ALXN2022, ¶94.) Depending on the convention used and the stage of development, a POSA might understand that a particular name refers to a group of several related antibodies, or in other cases, that a specific non-proprietary name (*e.g.*, "eculizumab") or a brand name (*e.g.*, "SOLIRIS®") refers to a single, unique monoclonal antibody with one defined structure and one primary amino acid sequence. (ALXN2022, ¶¶ 94-103; ALXN2032, 10:9-11:17, 98:2-99:8, 100:3-24, 202:24-203:14.)

At early stages of development of a humanized monoclonal antibody, a POSA would have understood that informal research code names were commonly used, and typically referenced the original source mouse antibody from which the humanized antibody was generated (*e.g.*, "5G1.1"). (ALXN2022, ¶95; ALXN2032, 98:2-99:8, 202:24-203:14.) A POSA would have understood that, depending on the context, these code names could potentially refer to a number of

different structures or sequences. (ALXN2022, ¶95; ALXN2032, 98:2-99:8, 159:1-10, 202:24-203:14.)

In contrast, after a specific humanized monoclonal antibody with a single, unique sequence has progressed into clinical development, it may be assigned a "non-proprietary" name (*e.g.*, "eculizumab") by authorities including INN and USAN. (ALXN2022, ¶97.) A POSA would have understood that these non-proprietary names with respect to humanized monoclonal antibodies would refer to one – and only one – specific antibody as defined by its unique amino acid sequence. (ALXN2022, ¶¶100-101, 120; ALXN2032, 10:9-11:17, 98:19-99:8, 100:3-10; ALXN2046, 1; ALXN2045, 1210.) The same would be true when, as the product neared FDA submission, the research sponsor would propose a unique branded trade name (*e.g.*, "SOLIRIS®"). (ALXN2022, ¶102.)

C. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" to be the IgG4 Monoclonal Antibody of Thomas

As of March 15, 2007, a POSA would have understood that a unique humanized monoclonal antibody named "eculizumab," that specifically targets human C5 and prevents its cleavage, had been developed. (ALXN2022, ¶¶118-123; AMG1047, 2559 (citing Thomas, AMG1023).)

But the POSA as of March 15, 2007 would ***not*** have known that "eculizumab" had the sequence claimed in the '149 patent, including the uniquely-

engineered heavy chain constant region reflected in SEQ ID NO: 2. Rather, a POSA at that time would have believed that "eculizumab" contained an "***IgG4***" constant region – which is very different from the uniquely-engineered heavy-chain constant region recited in claim 1 of the '149 patent. (ALXN2022, ¶¶120-123; ALXN2032, 97:7-21.) Specifically, the literature regarding the development of "eculizumab" consistently described "eculizumab" by referencing Thomas (AMG1023). (ALXN2022, ¶¶120-123, 139, 205-208; ALXN2032, 125:13-126:9, 128:20-129:10, 192:13-22, 160:18-162:12.) Thomas, in turn, detailed the design and testing of a full-length, ***IgG4***-isotype humanized antibody ("humanized 5G1.1") with anti-C5 affinity, specificity, and complement-blocking activity comparable to the original mouse "5G1.1" antibody. (AMG1023, 1396-99; ALXN2022, ¶123; ALXN2032, 242:21-243:4.)

As the following table illustrates, a POSA would have had no doubt that "eculizumab" was Thomas's IgG4-isotype humanized antibody, because the pertinent literature consistently and unambiguously said so:

Table 1: References to "Eculizumab" as Thomas's Humanized IgG4 Antibody

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hillmen (AMG1004) at 553 – Phase II clinical trial for treatment of PNH	"***Eculizumab is*** a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components." (Citing ***Thomas,*** Ref. No. 15)
Hill (AMG1047) at 2559 – 52-week extension of Hillmen Phase II clinical trial	"***Eculizumab is*** a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage." (Citing ***Thomas***, Ref. No. 9)
Hillmen 2006 (AMG1012) at 1234 – pivotal Phase III clinical trial for treatment of PNH,	"***Eculizumab (Soliris, Alexion Pharmaceuticals) is*** a humanized monoclonal antibody directed against the terminal complement protein C5." (Citing ***Thomas***, Ref. No. 13)
Hill 2007 (ALXN2028) – post-Phase III case report for PNH patient	"***Eculizumab is*** a novel humanized monoclonal antibody directed against the complement protein C5." (Citing ***Thomas***, Ref. No. 6)

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Bell (AMG1005) at [0052] – Phase II clinical studies described in Hillmen and Hill	States that "[m]ethods for the preparation of h5G1.1-mAb" are described in ***Thomas***, and that "[t]he antibody h5G1.1-mAb is currently undergoing clinical trials under the name ***eculizumab***."
Kaplan (AMG1021) at 1018	States that "***Eculizumab*** (5G1.1), under development by Alexion Pharmaceuticals Inc. is a humanized C5 inhibitory monoclonal antibody (mAb)," and cites ***Thomas*** for the synthesis and complement-blocking activity of "intact humanized 5G1.1 antibody" or "humanized 5G1.1"
Brekke (AMG1019) at 56	"***Eculizumab*** (5G1.1; Alexion Pharmaceuticals) ***is*** a humanized monoclonal antibody that prevents the cleavage of human complement component C5" (citing ***Kaplan***, Ref. No. 31, which in turn cites to ***Thomas***)
Pierangeli (AMG1020) at 2123	Stating that "***eculizumab*** has been shown to prevent C5 activation in humans and to have beneficial effects in patients with [PNH]" (citing to ***Hillmen***, Ref No. 18, which in turn cites to ***Thomas***)

Looking at this literature, a POSA would have believed that Thomas's IgG4 antibody was the ***only*** full-length humanized antibody shown to bind C5 and prevent its cleavage, tested for safety and efficacy in treating PNH, and submitted to the FDA for marketing approval.[2] In Thomas, a POSA would have seen the extensive work in rationally designing an "intact" humanized monoclonal antibody preserving the anti-C5 activity of the "5G1.1" mouse antibody, using an IgG4 isotype. (AMG1023, 1393-99; ALXN2022, ¶123; ALXN2032, 242:21-243:4.) And, prior to March 15, 2007, a POSA would have seen that "eculizumab" – consistently identified as Thomas's IgG4 antibody – was shown to be safe and effective in treating PNH, and was submitted for FDA and European approval under the trade name SOLIRIS®. (*See, e.g.*, AMG1004, AMG1047, AMG1012, ALXN2028; AMG1005, ¶¶[0052], [0081-0096]; ALXN2022, ¶¶121-123.)

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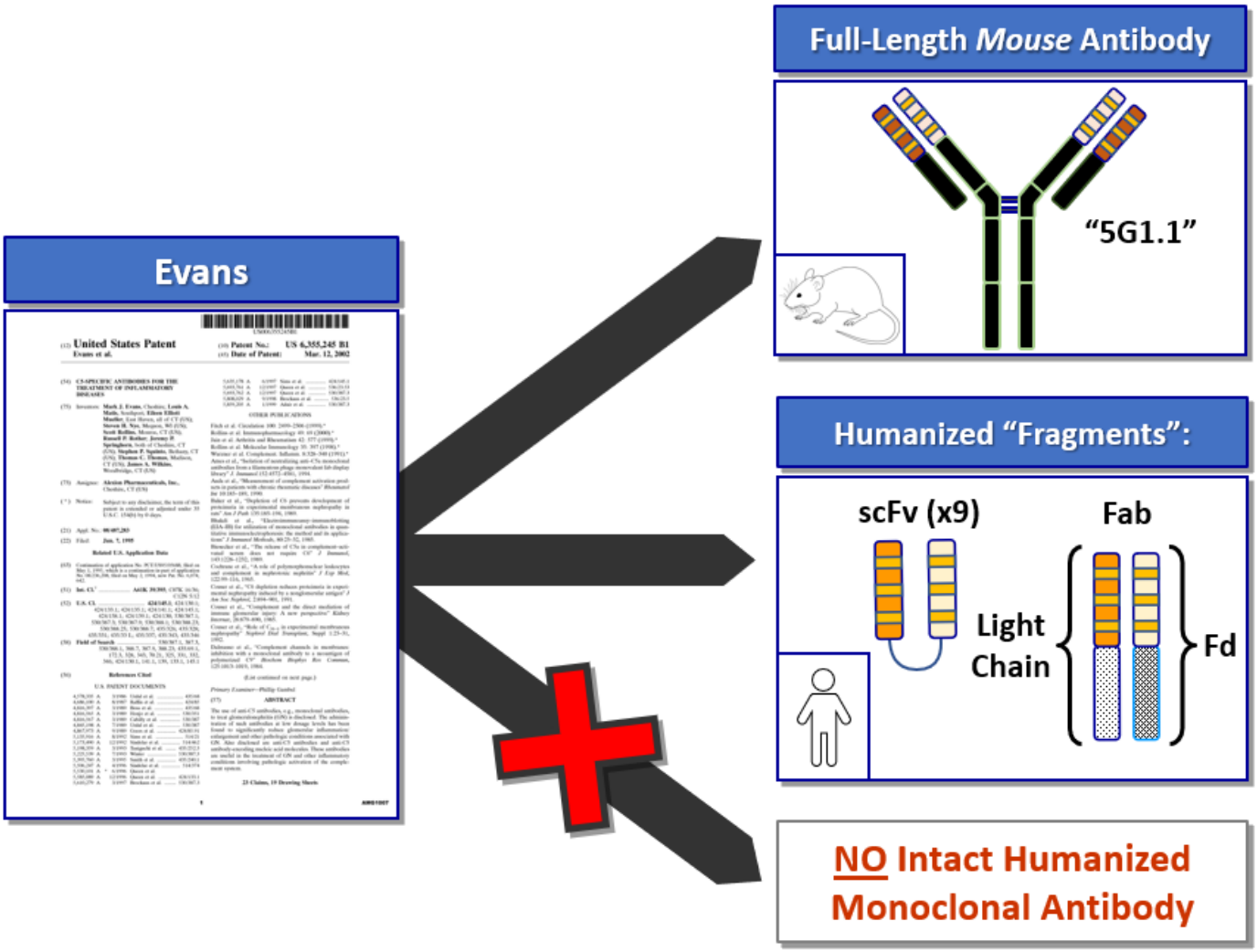
[2] Thomas also does not disclose the specific light chain amino acid sequence recited in SEQ ID NO: 4 of the '149 patent. In particular, the light chain variable region sequence provided by Thomas differs from SEQ ID NO: 4 of the '149 patent at amino acid position 38, flanking light chain CDR1. (*Compare* AMG1023 at 1392, 1396 (identifying position 38 as "R" (arginine)) *with* AMG1001 at col. 35, SEQ ID NO 4 (identifying position 38 as "Gln" (glutamine).)

In contrast to Thomas and the literature regarding "eculizumab" that followed Thomas, a POSA would have understood that Evans (AMG1007) did ***not*** disclose "eculizumab." (ALXN2022, ¶¶124-130.) Rather, a POSA would have understood that Evans described an earlier stage of research that predated the design of the intact, full-length humanized antibody "eculizumab" – because Evans did ***not*** disclose any full-length humanized antibodies. (ALXN2022, ¶¶124-128, 191, 198-199; ALXN2032, 163:12-15, 169:13-18.) At most, a POSA would have read Evans as a precursor to the research that resulted in "eculizumab."

As Dr. Balthasar agreed at deposition, the only full-length antibody described in Evans (AMG1007) is the "5G1.1" mouse antibody, which Evans obtained from the "5G1.1" hybridoma. (AMG1007, 19:47-49, Figs. 18-19; ALXN2032, 165:5-21, 169:13-18; ALXN2022 ¶¶125-128.) Evans further describes the researchers' characterization of the "5G1.1" mouse antibody, including its binding affinity, *in vitro* activity blocking complement in hemolytic assays, and the sequencing and cloning of the variable regions of the "5G1.1 mouse antibody." (AMG1007, Examples 7-10; ALXN2022 ¶125; ALXN2032, 165:5-169:23.) But Evans provides no such information for a full-length ***humanized*** antibody derived from the "5G1.1" mouse antibody – which a POSA would have understood would have a different amino acid sequence and different

clinical properties from the mouse antibody. (ALXN2022 ¶126; ALXN2032, 163:12-15, 169:24-170:4.)

To the extent Evans described "humanization" work based on the "5G1.1" mouse antibody, it was the development of recombinant "fragments" – scFv or Fab – that did ***not*** contain an intact heavy chain constant region, let alone the uniquely-engineered heavy chain constant region reflected in SEQ ID NO: 2 of the '149 patent. (AMG1007, Example 11; ALXN2022 ¶126.) For example, Evans described nine different humanized "scFv" fragments, which are recombinantly-produced molecules containing two variable regions connected by a linker, with no constant region (AMG1007, 43:6-14, 43:62-45:4), and humanized "Fab" fragments that also lack the "Fc" portion (regions CH2 and CH3) of an intact antibody (AMG1007, 43:21-61). (ALXN2022 ¶126.) Notably, the humanized Fab fragments of Evans have ***different*** heavy chain sequences ("Fd," Evans SEQ ID NOs: 11 and 12) from the non-prior art SEQ ID NO: 2 of the '149 patent, including in "CH1" constant region. (ALXN2022 ¶129.) The following figure illustrates how a POSA would have understood what Evans did disclose – a mouse antibody and humanized "fragments" – and what Evans did not disclose, *i.e.*, an intact humanized monoclonal antibody:



D. The Structure and Sequence of SOLIRIS® Was *Not* Known Prior to March 15, 2007

Today, but ***not*** before the priority date for the '149 patent, it is known that SOLIRIS® has the specific amino acid sequence recited in claim 1 of the '149 patent, namely, "a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." A POSA prior to the '149 patent, however, would not have known of any antibody consisting of SEQ ID NOs: 2 and 4, and would

not have reasonably expected that such an antibody would bind to C5 or would have any therapeutic application in humans.

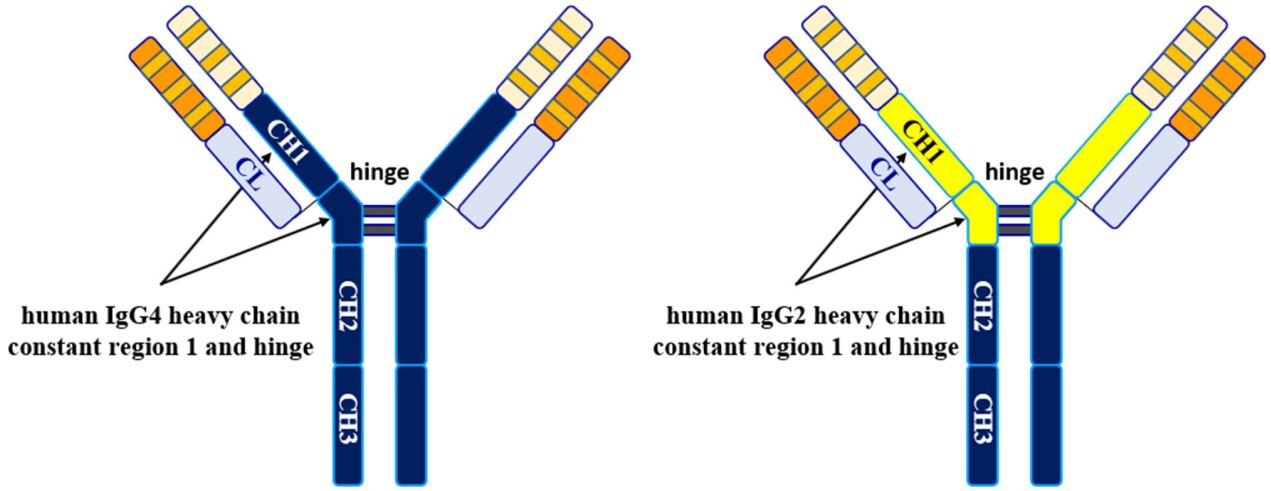
Today, but ***not*** prior to March 15, 2007, it is known that SOLIRIS® is a unique antibody that is ***very different*** from the humanized IgG4 antibody described in Thomas. As understood today, the heavy chain of SOLIRIS® (SEQ ID NO: 2) features a non-naturally occurring, uniquely-engineered constant region – containing sequences from both human IgG2 and IgG4 – that was designed by scientists at Alexion and was thoroughly tested in human clinical trials. (ALXN2022 ¶¶133-136.)

Notably, SOLIRIS® was the first FDA-approved product containing Alexion's uniquely-engineered heavy chain constant region. A POSA would not have been aware of any published clinical testing showing that an antibody with this uniquely-engineered constant region would be therapeutically useful and suitable for human administration.

The presently-known structure of SOLIRIS® reflected in claim 1 of the '149 patent is shown below in comparison to the IgG4 isotype antibody described in Thomas, which the literature prior to March 15, 2007 would have taught a POSA was "eculizumab." The figure depicts how, unlike the IgG4 antibody of Thomas, the claimed antibody uses the CH1 and "hinge" regions of IgG2, thereby providing

a meaningfully different antibody than that identified in the literature citing to Thomas.

Figure 2: **Left** – Structure of the IgG4 isotype antibody referenced to as "eculizumab" in the literature as of March 15, 2007
Right – Structure of SOLIRIS®, having a non-naturally occurring, protein-engineered isotype



Amgen's and Dr. Balthasar's arguments fail because they are based on the erroneous assumption that a POSA would have understood "eculizumab" to contain "a hybrid IgG2/IgG4 constant region." (*See, e.g.*, Petition, 15-16, 56; AMG1002 ¶¶ 42, 45, 54.) That assumption improperly ignores the overwhelming evidence that directed a POSA back then to look to Thomas for the structure of "eculizumab." (*See* Section II.C above.) Instead, to support its assumption that a POSA would have known that "eculizumab" contained an IgG2/IgG4 constant region, Amgen relies on a ***single***, ambiguous sentence in just one document –

Tacken (AMG1034)[3] – regarding an "isotype control antibody." But a POSA looking for the structure of "eculizumab" would not have considered, and certainly would not have credited, Tacken above the consistent, clear statements in earlier and later publications that expressly identified "eculizumab" as the IgG4 antibody of Thomas.

As Dr. Balthasar admitted, Tacken is the ***only*** document on which he relies dated prior to March 15, 2007 that purportedly associated "eculizumab" with a hybrid IgG2/IgG4 constant region. (ALXN2032, 104:14-20.) But unlike the clinical literature discussed in Section II.C above, Tacken did not concern the study of "eculizumab" in binding C5, blocking C5 cleavage or treating conditions such as PNH. (ALXN2022, ¶¶140-150; ALXN2032, 72:23-73:2, 73:12-74:1, 74:16-21.) Rather, Tacken involved the study of an entirely different antibody (the "hD1" antibody) with a wholly different purpose: directing antigens to a dendritic cell receptor for purposes of developing improved vaccinations. (AMG1034, 1278-79, 1283-84.)

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[3] Notably, Amgen does not rely on Tacken (AMG1034) as the basis for any of its five Grounds alleging anticipation or obviousness of the '149 patent.

Nothing in Tacken contradicted the consistent teaching of the prior art ***as a whole*** that "eculizumab" had an IgG4 constant region. In a single sentence identifying an "isotype control antibody" for use in studies of the "hD1" antibody directed to dendritic cells, Tacken states the following (including a citation to ***Thomas*** as Ref. No. 19):

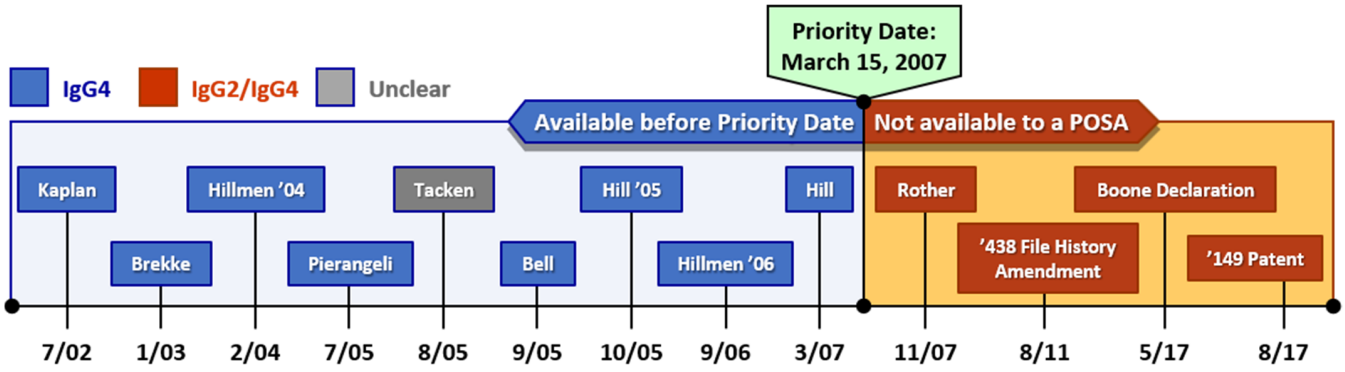
> An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[19]

(AMG1034, 1279.) A POSA reading that isolated, unclear statement would not have been dissuaded from the consistent, clear teaching in the literature as of March 15, 2007 (both before and after Tacken's publication) identifying "eculizumab" and "SOLIRIS®" as the ***IgG4*** antibody of Thomas. (*See supra* Table 1; ALXN2022, ¶¶140-150.) A POSA would have seen substantial ambiguity in that statement. Not only does Tacken misspell "eculizumab," but it uses multiple conflicting and undefined terms – including "h5G1.1-mAb," which could refer to a class of various humanized antibodies; and "5G1.1," which can refer to many things, including the original "5G1.1" mouse antibody from the "5G1.1" hybridoma. (ALXN2022, ¶143; ALXN2032, 98:2-99:8, 159:1-10; 202:24-203:14.) Further, a POSA would have seen Tacken's citation to Thomas's IgG4

antibody (Ref. No. 19) for "eculizamab" [sic] as inconsistent with its reference to an IgG2/IgG4 isotype control antibody. On balance, the ambiguous, passing reference in Tacken would not have led a POSA to "understand" that the clinically tested "eculizumab" antibody has an "IgG2/IgG4" constant region.

Amgen's myopic focus on the isotype control antibody of Tacken, to the exclusion of all other prior art information, is also not tenable because at least four prior art documents published ***after*** Tacken confirmed a POSA's belief as of March 15, 2007 that the clinically-tested "eculizumab" antibody was the ***IgG4*** antibody of Thomas. (ALXN2022, ¶¶145, 150.) For example, the Hill clinical study was published two months after Tacken in the same journal (Blood), and stated that "[e]culizumab is" the antibody of Thomas. (AMG1047, 2559 (Ref. No. 9); ALXN2032, 113:14-21, 114:19-115:10.) Bell, published a month after Tacken, likewise pointed to Thomas for methods of making "eculizumab," and made no mention of hybrid IgG2/IgG4 antibodies. (AMG1005, ¶[0052]; ALXN2032, 160:18-162:11.) The Hillmen 2006 Phase III study, published more than a year after Tacken in the New England Journal of Medicine, and the Hill 2007 case report, published on March 1, 2007, likewise both stated that "eculizumab is" Thomas's IgG4 isotype antibody. (AMG1012, 1234 (Ref. No. 13); ALXN2028, 31 (Ref. No. 6); ALXN2032, 116:16-117:1.)

As the following timeline figure illustrates, the ***only*** plausible conclusion a POSA could have reached in view of the entire contents of the art was that "eculizumab" was the IgG4 antibody of Thomas, and the ambiguous statement in Tacken (a publication having nothing to do with C5 binding) was either supportive of that understanding – as Tacken cites Thomas – or otherwise mistaken. (ALXN2022, ¶¶146, 150.) *See, e.g.*, *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 882-883 (Fed. Cir. 1998) (the "***entire contents of the prior art***" must be considered in determining whether the art showed a trend towards the claimed invention).



E. Overview of the ’149 Patent

The ’149 patent issued on August 15, 2017 from U.S. App. No. 15/284,015, filed on October 3, 2016, and claims priority to PCT/US2007/006606, filed on March 15, 2007. The patent has one claim:

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

(AMG1001, 39:1-4.).

Claim 1 of the ’149 patent recites the complete amino acid sequence for SOLIRIS® (eculizumab): the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001, cols. 31-33, 35.) Claim 1 of the ’149 patent further requires that the claimed antibody is “[a]n antibody that binds C5.”

The ’149 patent discloses that the claimed antibody binds C5, and provides Phase III clinical data from the “TRIUMPH” study confirming that the claimed antibody is safe and effective for treating PNH, and identifying the safe and effective dosing regimen for that use. (AMG1001, abstract, 3:4:63-67, 19:50-28:35.)

F. Prosecution History of the ’149 Patent and Related Applications

In prosecution leading to issuance of the ’149 patent, as well as prosecution of related U.S. Patent Nos. 9,725,504 (“the ’504 patent”) and 9,719,880 (“the ’880 patent”), the Examiner considered much of the same art that Amgen now asserts. The Examiner made findings undermining Amgen’s positions here, including that (1) none of the art recited an antibody comprising SEQ ID NOs: 2 and 4, (2) a POSA “would not have been easily guided to mak[e] antibodies with these recited sequences,” and (3) SOLIRIS® and its unique sequence was not “accessible to the public” as of March 15, 2007. (AMG1015, 772.)

For example, in finding claim 1 of the ’149 patent to be novel and nonobvious, the Examiner expressly discussed Amgen’s asserted references Hillmen 2004 (AMG1004) and Evans (AMG1007) as a basis for rejection, before ultimately finding claim 1 to be allowable over the art. (*See, e.g.*, AMG1015, 486-487, 596-598). The Examiner also considered Amgen’s asserted references Hill (AMG1047) and Bell (AMG1005); U.S. Patent No. 7,482,435 (ALXN2016) (the parent to, and cumulative of, Bowdish (AMG1006)); and “Mueller II” (AMG1031), which is cumulative of Mueller (AMG1008). (*See, e.g.*, AMG1015, 489-490, 497, 504, 506.) Alexion did not “mislead” the Patent Office or fail to disclose references pertaining to Amgen’s arguments here.

Notably, the Examiner confirmed a central fact that Amgen ignores: Hillmen cites to ***Thomas*** (*i.e.*, "reference number 15" of Hillmen) as "disclosing more information about eculizumab." (AMG1014, 559, 623 (citing AMG1023); *see also* AMG1015, 596 ("Hillmen ... teaches that 'eculizumab' is a recombinant humanized antibody that binds to C5 ... and cites ***Thomas***."). Ultimately, the Examiner agreed that the prior art did not disclose or suggest the specific claimed antibody sequence of the '149 patent. (AMG1015, 772; *see also* AMG1014, 790.)

The Examiner also credited the Declaration of Dr. Laural Boone (AMG1015, 734-741 ("the Boone Declaration") as showing that Alexion's clinical studies of the claimed antibody did not disclose its sequence or render it publicly accessible. (AMG1015, 772-73.) The Examiner relied on, among other things, Dr. Boone's showing that "neither doctors nor patients had any knowledge of the ... claimed sequences of the antibody used in the studies." (AMG1015, 738-741 ¶¶ 6-13, 772-773.) While it is known ***today*** that SOLIRIS® as used in these studies had the claimed sequence of SEQ ID NOs: 2 and 4 (AMG1015, 738 ¶ 6), a POSA as of March 15, 2007 would have only been guided by the teachings of the published literature that "eculizumab" had the IgG4 structure of Thomas.

III. PERSON OF ORDINARY SKILL IN THE ART OF THE '149 PATENT

Amgen contends that a POSA would have had "an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a

related discipline, with **at least two years of experience in the field**," and that a POSA would have had "skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics." (Petition, 20-21.)

Alexion does not dispute Amgen's POSA definition, except to clarify – as the Board accepted (Paper No. 15, 10-11) – that the POSA would have **at least two years of experience in engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry**. (ALXN2022, ¶¶25-26.)

IV. AMGEN'S PETITION FAILS TO SHOW UNPATENTABILITY OF CLAIM 1 OF THE '149 PATENT

A. Amgen's Grounds 1 and 2 Fail Because Amgen Cannot Show that Claim 1 Was Anticipated by Hillmen or Hill

Amgen's Grounds 1 and 2 contend that claim 1 of the '149 patent was anticipated by the clinical trial publications Hillmen (AMG1004) or Hill (AMG1047), respectively. As the Board recognized, Amgen's Grounds 1 and 2 fail, because Amgen cannot show how either Hillmen or Hill disclosed the claimed antibody of the '149 patent.

1. Hillmen and Hill Did Not Disclose an Antibody "Comprising a Heavy Chain Consisting of SEQ ID NO: 2 and a Light Chain Consisting of SEQ ID NO: 4"

Amgen's Grounds 1 and 2 fail because neither Hillmen nor Hill expressly or inherently discloses all the elements recited in claim 1 of the '149 patent. *See, e.g.*,

Therasense, Inc. v. Becton Dickinson & Co., 593 F.3d 1325, 1332 (Fed. Cir. 2010) ("Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim.").

In particular, as the Board recognized, both Hillmen and Hill fail to disclose an antibody comprising the specific amino acid sequence recited in claim 1 of the '149 patent. (Paper No. 15, 24-27.) Simply put, there were ***no amino acid sequences*** for "eculizumab" disclosed anywhere within the four corners of the Hillmen and Hill publications. (ALXN2022, ¶¶172-181.) To the extent Hillmen and Hill provided any guidance about the structure of "eculizumab," they identified "eculizumab" by reference to Thomas (AMG1023) – which in turn described a humanized monoclonal antibody with an "***IgG4***" heavy chain constant region having a very different amino acid sequence from the '149 patent's SEQ ID NO: 2. (*See supra* Section II.C.) At deposition, Dr. Balthasar conceded that Hillmen's and Hill's statements regarding what "eculizumab is" cited to Thomas; and he was unable to identify ***any*** disclosure within Hillmen, Hill, or their cited references suggesting that "eculizumab" had a hybrid IgG2/IgG4 constant region, rather than the IgG4 constant region of the cited Thomas reference. (ALXN2032, 123:8-15, 125:13-126:11, 126:19-23, 127:19-128:1, 128:20-129:10, 132:7-12, 134:9-21.)

Accordingly, neither Hillmen nor Hill, including their references to "eculizumab," disclosed each and every element of claim 1 of the '149 patent.

2. Neither Hillmen nor Hill Inherently Disclosed the Unique, Non-Public Amino Acid Sequence of SOLIRIS® Recited in Claim 1 of the '149 Patent

To supply the claimed elements of SEQ ID NOs: 2 and 4 that are plainly missing from Hillmen and Hill, Amgen admittedly must go ***outside*** the four corners of the references themselves, and turns to a either patent prosecution document created in 2017 that indisputably was not prior art available to a POSA as of March 15, 2007, or to amino acid sequences that Amgen mixes and matches from extraneous documents (Bowdish, Mueller, and Evans) that were not cited or referenced anywhere in Hillmen and Hill. (Petition, 25-26, 32-34; (ALXN2022, ¶¶179-180.)

For example, Amgen alleges inherent anticipation of claim 1 on the ground that ***today*** – years after the '149 patent's March 15, 2007 priority date – it is known that the clinical studies underlying the Hillmen and Hill publications ***actually*** used an antibody with a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4. (*See, e.g.*, Petition, 25 (citing the May 11, 2017 Declaration of Dr. Laural Boone, AMG1015, 734-741).) But Amgen is mistaken on the law. The mere naming of an investigational product (*e.g.*, "eculizumab") in a prior art publication does ***not*** inherently anticipate later-filed patent claims

detailing the specific structure or composition of that product (*i.e.*, SEQ ID NOs: 2 and 4), if a POSA could not have ***necessarily*** determined the later claimed structure/composition from the information publicly available as of the priority date. *See, e.g.*, *Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-83 (Fed. Cir. 2018). Likewise, post-filing information showing that the later-claimed antibody sequence was actually used in the studies underlying prior art clinical publications is insufficient to give rise to inherent anticipation, when those prior art publications would have guided a POSA to a different, unclaimed antibody sequence. *See, e.g.*, *id.*; *Bayer CropScience LP v. Syngenta Ltd.*, IPR2017-01332, Paper 15 at 3-6 (Apr. 2, 2018).

B. Amgen's Ground 3 Fails Because Amgen Cannot Show that Claim 1 Was Anticipated by Bowdish

Amgen's Ground 3 contends that claim 1 of the '149 patent was anticipated by Bowdish (AMG1006). But Amgen cannot show how Bowdish disclosed all of the elements of claim 1 of the '149 patent, including "[a]n antibody that binds C5" having the specific, uniquely-engineered amino acid sequence recited in the claim. *See, e.g.*, *Therasense*, 593 F.3d at 1325. There is simply no disclosure in Bowdish – even if fully combined with Evans (AMG1007) – of an antibody having the full sequence claimed in the '149 patent. Amgen fails to show why Evans should be considered at all, when Bowdish incorporated not Evans but a different document

(the "'283 application") that Amgen neglected to consider or introduce in this proceeding.

Even if Evans is considered in the '283 application's place, Amgen overreads Bowdish's limited incorporation by reference for "[c]onstruction of 5G1.1," a mouse antibody with a very different sequence and structure from the claimed antibody of the '149 patent. Even if the entirety of Evans was improperly considered to be incorporated by reference, Amgen exceeds the bounds of anticipation by culling and recombining bits and pieces from Bowdish and Evans to reconstruct the claimed sequence of the '149 patent. This cannot meet the requirement "for an anticipatory reference to show all of the limitations of the claims ***arranged or combined in the same way*** as recited in the claims…." *Net MoneyIN, Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1369-70 (Fed. Cir. 2008); *see also id.* at 1371 ("[I]t is not enough that the prior art reference … includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.").

Further, Amgen fails to show how Bowdish disclosed or enabled the element of "[a]n antibody that binds C5" as required by claim 1 of the '149 patent. In particular, Amgen has pointed to nothing in Bowdish or Evans, even in full combination, that disclosed anything about the C5 binding properties of an antibody comprised of SEQ ID NO: 2 and SEQ ID NO: 4 as recited in claim 1.

1. Bowdish Did Not Disclose or Incorporate by Reference an Antibody Comprising SEQ ID NO: 2 and SEQ ID NO: 4

Amgen concedes that Bowdish alone does not disclose an antibody "comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4" as recited in claim 1. As Dr. Balthasar admitted, Bowdish does not disclose the entire amino acid sequence recited in claim 1 of the '149 patent; and the compound consisting of the amino acid sequences listed in Bowdish Figures 13A and 13B is not the claimed antibody of the '149 patent. (ALXN2032, 181:17-23, 182:21-183:1; (ALXN2022, ¶185.)

Amgen also does not contend that Bowdish alone expressly discloses "[a]n antibody that binds C5" as recited in claim 1 of the '149 patent. Bowdish concerned using an antibody – ***any*** antibody – as a "scaffold" to house a peptide (*e.g.*, the hormone TPO), thereby providing greater stability and longer half-life for the peptide *in vivo*. (AMG1006, ¶¶[0005]-[0006]; ALXN2022, 159-161, 200; AMG1002, ¶50.) The assays reported in Bowdish had nothing to do with C5 binding or blocking complement-mediated lysis. Rather, Example 4 of Bowdish assessed the binding of TPO-mimetic peptide (presented on an antibody scaffold) with a TPO receptor (the "cMpl receptor") – a biological interaction that is not part of the complement pathway and has nothing to do with cleavage of C5.

(AMG1006., ¶[0192]; ALXN2022, ¶¶159-161, 200.) Those two facts should end the inquiry on anticipation.

Conceding that Bowdish alone does not disclose the invention recited in claim 1 of the ’149 patent, Amgen’s Ground 3 depends wholly on Bowdish’s “incorporation by reference” of limited subject matter from “U.S. Application Ser. No. 08/487,283” (“the ’283 application”) for “[c]onstruction of 5G1.1.” (Petition, 37-40 (citing AMG1006, ¶[0191]).) But that limited incorporation by reference does not save Amgen’s Ground 3. First, Amgen’s anticipation arguments based on Bowdish fail for lack of proof, because – as Dr. Balthasar conceded at deposition – Amgen did not consider or introduce into the record the “’283 application” that Bowdish purports to incorporate. (AMG1006 ¶ [0191]; ALXN2032, 191:2-11, 192:7-11, 208:3-8.) Instead, Amgen combines Bowdish with a different document that Bowdish did ***not*** incorporate by reference – the Evans patent (AMG1007). (Petition, i, 37-40; ALXN2032, 191:12-25, 192:7-13, 207:19-208:8.) While Evans (AMG1007) issued from the ’283 application, it is not the ’283 application itself, and Amgen’s failure to even ***consider*** the contents of the actual ’283 application referenced by Bowdish is fatal to its anticipation position in Ground 3.

Even using Evans (AMG1007) as a stand-in for the ’283 application – which Amgen cannot do – Amgen cannot show that Bowdish anticipates claim 1 of the ’149 patent. Amgen misreads Bowdish’s narrow reference to the ’283 application,

which does ***not*** support treating the two documents as merged in their entirety. Amgen further ignores the requirement that an anticipating reference "must ***clearly and unequivocally*** disclose the claimed invention or direct those skilled in the art to the invention without ***any*** need for picking, choosing, and combining various disclosures not directly related to each other." *Net MoneyIN*, 545 F.3d at 1371 (emphasis in original). In particular, Amgen disregards the ambiguity in Bowdish and its reference to the '283 application, and uses improper hindsight analysis to recombine select parts of Bowdish and Evans – which is not permitted in assessing anticipation. *See In re Ruschig*, 353 F.2d 965, 974 (C.C.P.A. 1965) (forbidding "the mechanistic dissection and recombination" of the prior art "to create hindsight anticipations with the guidance of an applicant's disclosures").

The only reference in Bowdish to the '283 application states: "Construction of 5G1.1 is described in U.S. Application. Ser. No. 08/487,283, incorporated by reference herein." (AMG1006, ¶[0191].) Amgen fails to show how that one reference could magically convert Bowdish into an anticipatory disclosure of claim 1 of the '149 patent. First, Bowdish's vague statement referencing the '283 application for "[c]onstruction of 5G1.1," without further explanation, is not effective to incorporate any specific material from Evans into Bowdish, because it fails the requirement that "the host document . . . identify with ***detailed particularity*** what specific material it incorporates and ***clearly indicate*** where that

material is found in various documents." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000).

Even if a POSA had attempted to make sense of Bowdish's reference to "[c]onstruction of 5G1.1 as described in [the '283 application]," it would not have led them to a clear and unequivocal disclosure of the invention claimed in the '149 patent. A POSA reading Bowdish would have understood that its incorporation was ***limited*** to the portion of the Evans[4] describing the "[c]onstruction of 5G1.1." (ALXN2022 ¶¶162-163, 187-190.) In turn, a POSA looking to Evans for "[c]onstruction of 5G1.1" would have been directed to Evans's description of a ***mouse*** antibody – "the 5G1.1 antibody" or "the 5G1.1 mAb", obtained from the original "5G1.1" hybridoma. (*See supra* 19; ALXN2022 ¶¶189-190.) For example, Evans explains that "[a] particularly preferred antibody of the invention is ***the 5G1.1 antibody*** (5G1.1, ***produced by the 5G1.1 hybridoma***, ATCC designation HB-11625)," and identifies Figs. 18 and 19 as disclosing the light

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[4] For ease of reference, we refer herein to "Evans" rather than the "'283 application," without any waiver of Alexion's position that Bowdish incorporates by reference only limited portions of the '283 application (not in evidence in this proceeding), and does not at all incorporate or reference Evans (AMG1007).

chain and heavy chain variable regions of "***the antibody 5G1.1***." (AMG1007, 19:47-49, Figs. 18-19; ALXN2032, 165:5-21.)

This combination of Bowdish with Evans's description of the "5G1.1" mouse antibody cannot anticipate claim 1 of the '149 patent, because it fails to "describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Wasica Finance GmbH v. Continental Automotive Sys., Inc.*, 853 F.3d 1272, 1284 (Fed. Cir. 2017). As the following figures illustrate, a comparison of the sequences for Evans's "5G1.1" mouse antibody variable regions (AMG1007, Figs. 18-19) or the whole "5G1.1" mouse antibody (ALXN2026; ALXN2087) with the sequences for Bowdish's TPO-mimetic compound (AMG1006, Figs. 13A and 13B) would have revealed a mismatch in amino acids ***beyond*** those that Bowdish identified as the TPO-mimetic peptide insert (ALXN2022 ¶¶214-215):

```
Bowdish13A:  QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGE
             |||| |||||  ||||||| |||| |||||||||||  | || |||| ||
   Evans19:  QVQLQQSGAELMKPGASVKMSCKATGYIFSNYWIQWIKQRPGHGLEWIGE

Bowdish13A:  ILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLP
             |||||||||||||||||    | |||  | || |||| ||| |||||||||
   Evans19:  ILPGSGSTEYTENFKDKAAFTADTSSNTAYMQLSSLTSEDSAVYYCAR--

Bowdish13A:  IEGPTLRQWLAARAP-----VWGQGTLVTVSS
             ||||||||      ||||||||| || |||||
   Evans19:  --------YFFGSSPNWYFDVWGAGTTVTVSS
```

```
Bowdish13B:  DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYG
             |||||||| |||||||  |||||||||||||||||||| | || | |||||
   Evans18:  DIQMTQSPASLSASVGETVTITCGASENIYGALNWYQRKQGKSPQLLIYG

Bowdish13B:  ATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQ
             |||||||  |||||||||    | |||| | | |||||||||||||||||
   Evans18:  ATNLADGMSSRFSGSGSGRQYYLKISSLHPDDVATYYCQNVLNTPLTFGA

Bowdish13B:  GTKVEIK
             ||| | |
   Evans18:  GTKLELK
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<u>Top</u>: Bowdish Figure 13A (SEQ ID NO: 67) compared to Evans Fig. 19

<u>Bottom</u>: Bowdish Fig. 13B compared to Evans Fig. 18

```
Bowdish13A:  --------------------QVQLVQSGAEVKKPGASVKVSCKASGYIFSN
                                 |||| |||||  ||||||| |||| ||||||
   5G1.1HC:  MEWTWVFLFLLSVTAGVHSQVQLQQSGAELMKPGASVKMSCKATGYIFSN

Bowdish13A:  YWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVYM
             |||||  | || |||| |||||||||||||||||    | |||  | ||
   5G1.1HC:  YWIQWIKQRPGHGLEWIGEILPGSGSTEYTENFKDKAAFTADTSSNTAYM

Bowdish13A:  ELSSLRSEDTAVYYCARLPIEGPTLRQWLAARAP-----VWGQGTLVTVS
              |||| |||||||||||                |||||||||  || ||||
   5G1.1HC:  QLSSLTSEDSAVYYCAR----------YFFGSSPNWYFDVWGAGTTVTVS

Bowdish13A:  SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
             || |  ||| ||||    |  |   |||||| |||||||  |||| | ||
   5G1.1HC:  SAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSG

Bowdish13A:  VHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE
             ||||||||||  || ||| ||| ||    |  |||| |  | |||||  |
   5G1.1HC:  VHTFPAVLQSD-LYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIE

Bowdish13A:  RK--CCVECPP--CPAPP-VAGPSVFLFPPKPKDTLMISRTPEVTCVVVD
                     |||  |||| |  ||||| |||| || |||  || |||||||
   5G1.1HC:  PRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVD

Bowdish13A:  VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
             ||  || ||  | |  |||| | |    || ||| |||| |   ||||
   5G1.1HC:  VSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMS

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

Bowdish13A:  TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS
             || |  | | || |||  ||  | ||| | |||||||| | || | | |
   5G1.1HC:  TCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKK

Bowdish13A:  RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
              | | |  |||| || |||| | || |   ||
   5G1.1HC:  NWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
```

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

In view of the mismatch between the sequences of Bowdish and the incorporated sequences of Evans, a POSA as of March 15, 2007 would have found Bowdish's reference to Evans to be at most, ambiguous, and certainly would not have understood Bowdish to clearly and unequivocally disclose an antibody consisting of SEQ ID NOS: 2 and 4 recited in claim 1 of the '149 patent. In particular, nothing in Bowdish's reference to the "5G1.1" mouse antibody of Evans would have indicated to a POSA that the "scaffold" antibody (whose sequence was not disclosed in Bowdish) used to generate Bowdish's TPO-mimetic compound was the specific antibody consisting of SEQ ID NOs: 2 and 4 of the '149 patent. ALXN2022, ¶¶162-163, 190.) Claim 1 of the '149 patent cannot be anticipated by such an ambiguous disclosure. *See, e.g.*, *Wasica Finance*, 853 F.3d at 1284 ("[A]mbiguous references do not, as a matter of law, anticipate a claim.").

Rather than acknowledge the limitations and ambiguity of Bowdish's reference to the '283 application, Amgen misconstrues the scope of that cross-reference, and disregards its limitations entirely. For example, Amgen attempts to rewrite the statement regarding "[c]onstruction of 5G1.1" to refer to "[c]onstruction of ***eculizumab***" (Petition, 6-7, 17), or construction of the antibody used as the "***scaffold***" for Bowdish's TPO-mimetic compound (Petition, 38; AMG1002, ¶ 94). There is no dispute that neither Bowdish nor Evans mention "eculizumab." ALXN2022 ¶¶124, 131, 185; ALXN2032, 199:9-17.) And reading

Bowdish as referencing Evans for "construction of eculizumab" or "construction of the scaffold antibody" would have made no sense, because Evans did not disclose the construction of ***any*** full-length, intact humanized monoclonal antibodies, let alone "eculizumab." (*See supra* 18-19.) As Dr. Balthasar admitted, "the 5G1.1 antibody" disclosed in Evans was a ***mouse*** antibody – and was the only full-length antibody that Evans disclosed. (ALXN2032, 165:5-169:23; *see supra* 19.)

Amgen's Ground 3 further fails because it relies on material from Evans that Bowdish did ***not*** clearly incorporate by reference. In particular, Amgen's Ground 3 depends upon the mixing and matching of Bowdish's sequences with sequences from Evans's "***scFvs***" – which are ***not*** the "5G1.1 antibody" of Evans, but rather are "fragments" produced by recombinant DNA technology containing only variable regions connected by a linker sequence.

Amgen is simply mistaken to the extent it contends that Bowdish may be combined with Evans ***in its entirety*** for purposes of assessing anticipation by Bowdish – as Dr. Balthasar admitted he was instructed by counsel. (ALXN2032, 189:23-191:1.) *See, e.g.*, *Schwarz Pharma, Inc. v. Warner-Lambert Co.*, 95 F. App'x 994, 998 (Fed. Cir. 2004) (an incorporation by reference referring to the "disclosure" of drug compounds did not also incorporate the drug compounds' synthesis or pharmaceutical compositions). Notably, when Bowdish intended to

incorporate other documents "in their entirety," it did so expressly (AMG1006, ¶ [0001]). Bowdish did not do so for Evans.

2. Bowdish, Even if Combined with Evans in its Entirety – Did Not Disclose, Either Expressly or Inherently, an Antibody with the Specific Sequences Recited in Claim 1 of the '149 Patent

Even if a POSA reading Bowdish were to consider the disclosures of Evans beyond those pertaining to construction of Evans's "5G1.1" mouse antibody – which the law does not allow – they still would not find a clear and unequivocal disclosure of the specific antibody recited in claim 1 of the '149 patent. *See Net MoneyIN*, 545 F.3d at 1371. Nor would it have been apparent to a POSA, as Amgen posits, that the "scaffold" antibody used to generate Bowdish's TPO-mimetic compound "***necessarily*** possessed the claimed sequences" of the '149 patent. (Petition, 35.) To the contrary, Amgen's anticipation argument fails here because it cannot show that the specific claimed antibody consisting of SEQ ID NOs: 2 and 4 was "***necessarily present,***" or, frankly, present at all, in the disclosure of Bowdish and its reference to the '283 application. *See, e.g.*, *Endo*, 894 F.3d at 1383; *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991).

Unlike a POSA, who would have had no clear picture of the structure and sequence of Bowdish's "scaffold" antibody, Amgen uses the benefit of its

hindsight knowledge of the ’149 patent to reconstruct that sequence from bits and pieces of Bowdish and Evans. Such selective mixing and matching from unconnected disclosures in hindsight is forbidden in anticipation analysis. (*See supra* 37-38.) In particular, Amgen attempts to prove its anticipation case by illustrating sequence alignments between, on the one hand, carefully selected sequences from Bowdish and Evans, and on the other hand, the sequences claimed in the ’149 patent. (Petition, 19, 36, 39, 43; AMG1002 Figs. 3-7, 10, 10-14.) But a POSA as of March 15, 2007 could not have done that analysis, because ***the ’149 patent was not available*** for a POSA to use as a point of comparison. (ALXN2032, 222:7-224:24; ALXN2022, ¶196.)

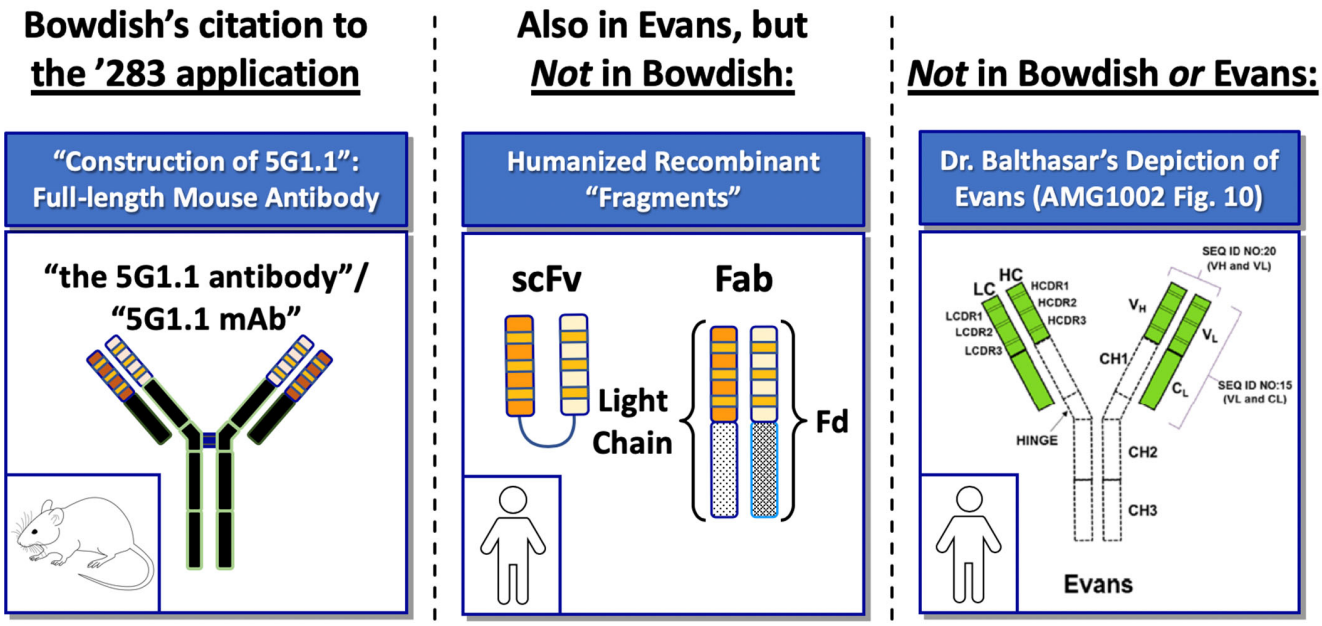
To the contrary, a POSA as of March 15, 2007 reading Bowdish and Evans together would have been left without knowing the precise structure of Bowdish’s “scaffold” antibody, and certainly would not have had a clear and unambiguous picture of the specific, unique sequence recited in claim 1 of the ’149 patent. Even if Amgen were correct that Bowdish guided a POSA to look to Evans for construction of the “scaffold” used to produce Bowdish’s TPO-mimetic compound (*e.g.*, Petition, 38; AMG1002 ¶ 94), the POSA would have come up empty-handed, because nothing in Evans disclosed ***any*** full-length antibodies, aside than the “5G1.1” mouse antibody. (ALXN2022, ¶191; *supra* 18-19.)

Further, if a POSA were to look elsewhere in Evans for "heavy chain CDR3" sequences not associated with the (undisclosed) Bowdish "scaffold" antibody, they still would not have ***necessarily*** arrived at the specific claimed sequence recited in claim 1 of the '149 patent. Rather, a POSA have seen that Evans provided for ***multiple*** possible definitions for that CDR sequence, and did not specify which, if any, would have been the "heavy chain CDR3" of the "scaffold" antibody referenced in Bowdish. (ALXN2022, ¶195.) For example, Evans described "minimal" and "maximal" definitions for the CDRs it disclosed, and also expressly allowed for CDRs comprising overlapping ranges of those minimal and maximal sequences. (AMG1007, 5:15-36.) Nothing in Bowdish or Evans would have clearly and unambiguously identified which, if any, of those sequences was the "heavy chain CDR3" featured in the "scaffold" antibody used to make Bowdish's TPO-mimetic compound – a full-length structure that is found nowhere in Evans. (ALXN2022, ¶195.)

Instead, Amgen incorrectly assumes that a POSA would have determined Bowdish's "scaffold" to have the presently-claimed sequence by combining sequences from Bowdish's TPO-mimetic compound with a CDR sequence for Evans's recombinant "***scFv***" fragments. (Petition, 38-40; AMG1002, ¶¶95-96.) Nothing in Bowdish referred to Evans for disclosure of scFv compounds, or would have guided a POSA to look to such recombinant fragments to understand the

sequence of the structurally distinct full-length "scaffold" antibody used to generate Bowdish's TPO-mimetic compound. (ALXN2022, ¶¶192-194, 198.) As discussed above, there is no dispute that a POSA would have understood scFvs to be very different structures from the full-length antibody from which Bowdish's TPO-mimetic compound was derived. (*See supra* 11-12.)

Accordingly, Amgen's "Figure 12," which purports to construct the claimed antibody of the '149 patent from sequences recombined from Bowdish and Evans, is misleading, because it improperly depicts Evans's "scFvs" as if Evans disclosed them as the variable regions of an intact, full-length antibody "Y" structure. As Dr. Casadevall's **Figure 8** demonstrates, a POSA would not have understood Evans's disclosures to be as Amgen depicted them in hindsight, but rather would have understood Evans to disclose (1) a full-length mouse antibody that differed in sequence and structure from Bowdish's "scaffold" antibody, and (2) recombinantly-generated humanized scFvs that were not associated with, or even derived from, Bowdish's "scaffold" antibody or any other full-length human or humanized antibody.



3. Bowdish Did Not Disclose "[A]n Antibody that Binds C5" Having the Sequence Claimed in the '149 Patent

Amgen further fails to show how Bowdish and Evans, even if combined in their entirety, would have disclosed or enabled the element of "[a]n antibody that binds C5" comprising the specific, uniquely-engineered amino acid sequence of claim 1 of the '149 patent. The element of "an antibody that binds C5" is a fundamental characteristic required by claim 1 of the '149 patent. (*E.g.*, AMG1002, ¶107 ("'[A]n antibody that binds C5' [is] required by claim 1 ….") *See In re Jasinski*, 508 Fed. App'x 950, 952 (Fed. Cir. 2013). But Bowdish, on its face, says nothing about C5 binding of either its TPO-mimetic compound or the "scaffold" used to generate it, and contains no discussion or data concerning C5

binding. (ALXN2022, ¶¶158-161, 211; ALXN2032, 174:2-176:6, 180:8-11, 181:5-15, 188:4-10.)

The required element of "[a]n antibody that binds C5" also was not disclosed or enabled by Bowdish's reference to the '283 application. The only antibody that Bowdish referenced from Evans, and that Evans further described as binding C5, was the ***mouse*** "5G1.1" antibody, which has a very different sequence and structure from the claimed antibody of the '149 patent. (*See supra* 18-19.) And even considering Evans in its entirety (which Bowdish did not instruct a POSA to do), nothing in Evans disclosed the structure or C5 binding properties Bowdish's "scaffold" antibody or ***any*** full-length antibody other than the mouse antibody. (*See supra* 18-21.)

Accordingly, even if the sequence of Bowdish's "scaffold" antibody were fully known, a POSA would still not have known that antibody to be "[a]n antibody that binds C5." As Dr. Casadevall explains, a POSA would not have been able to infer the C5 binding properties of a new, untested antibody structure from its amino acid sequence alone. (ALXN2022, ¶¶224-229.)

Bowdish's reference to the "5G1.1" antibody of Evans – a mouse antibody – would have taught a POSA nothing about whether Bowdish's structurally distinct "scaffold" antibody bound C5. (ALXN2022, ¶¶159-163, 214-215.) Likewise, Amgen's assertion that Evans "disclosed preparing different humanized C5-

binding antibodies referred to as '5G1.1' antibodies" (Petition, 38) is incorrect, because it is undisputed that Evans disclosed ***no*** full-length "humanized C5-binding antibodies," and the only full-length "5G1.1" antibody set forth in Evans was a mouse antibody – which would have taught a POSA nothing about the binding properties of the very different "scaffold" antibody of Bowdish. (ALXN2022, ¶¶214-215.)

Amgen also cannot show how Bowdish, even if fully combined with Evans, was enabling for "[a]n antibody that binds C5" with the specific amino acid sequence recited in claim 1 of the '149 patent. *See, e.g.*, *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. and Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003). Even if the entire claimed sequence could have been determined from Bowdish (which Amgen fails to show), a POSA would not have been able to reasonably predict whether that sequence – which was not characterized for C5 binding in Bowdish or Evans – would constitute an anti-C5 antibody. (ALXN2022, ¶200.)

C. Amgen's Ground 4 Fails Because Amgen Cannot Show that Claim 1 Would Have Been Obvious Over the Combination of Bell, Bowdish and Evans

Amgen's Ground 4 contends that claim 1 of the '149 patent would have been obvious over a combination of Bell (AMG1005), Bowdish (AMG1006) and Evans (AMG1007). Amgen's Ground 4 fails because it is founded in an incredible, impermissible hindsight-driven premise: that a POSA considering Bell's

description of "eculizumab" would have ignored what Bell ***actually*** taught about the structure of "eculizumab" – that it was the full-length IgG4-isotype antibody of Thomas – and would have instead turned to Bowdish (which Bell does not cite) and Evans, both which make no mention of "eculizumab" or any other full-length humanized monoclonal antibodies known to bind C5 or have any therapeutic utility. (Petition, 41-47.)

Without the benefit of hindsight, a POSA as of March 15, 2007 would have had ***no reason*** to select and combine the sequences from Bowdish and Evans that Amgen picks and chooses to recreate the claimed sequences of the '149 patent; would have had ***no motivation*** to make such a new, untested antibody with no known or reasonably predictable binding, biological or therapeutic properties; and would have ***no reasonable expectation*** that such a new untested antibody would be "[a]n antibody that binds C5," as claim 1 requires. (ALXN2022, ¶¶202-229.)

1. Bell Did Not Disclose the Claimed Sequence, and Would Not Have Motivated a POSA to Make the Claimed Antibody

To supply the claim element "[a]n antibody that binds C5," Amgen relies upon Bell for its disclosure of "eculizumab," which Bell identifies by that name. (Petition, 41-42; AMG1002, ¶105; ALXN2032, 145:9-14, 152:19-25.) According to Amgen's argument – which we do not dispute in this respect – a POSA as of March 15, 2007 would have specifically been motivated to make and use Bell's

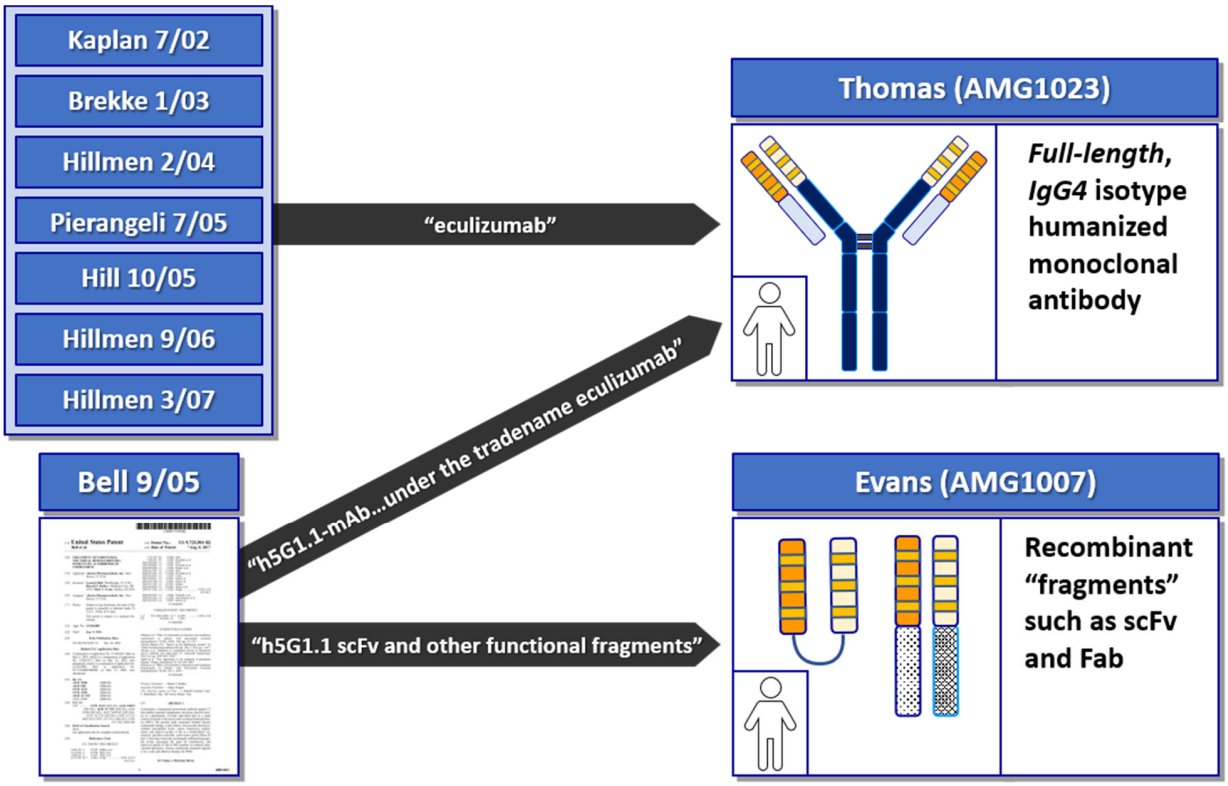
"eculizumab" antibody, in view of Bell's teaching that "eculizumab" binds C5, blocks its cleavage, and successfully treats PNH. (*See, e.g.*, AMG1002, ¶107; ALXN2032, 152:14-18, 153:1-11; 154:1-17; ALXN2022, ¶¶204-208.) For example, Dr. Balthasar admitted that Bell, along with Hillmen and Hill, motivated a POSA as of March 15, 2007 to "make and use the eculizumab antibody that they describe." (ALXN2032, 154:1-7.)

Amgen further concedes that – just like Hillmen and Hill – ***nothing*** in Bell disclosed the amino acid sequence for "eculizumab," or provided the specific amino acid sequence recited in claim 1 of the '149 patent. (Petition, 42; AMG1002, ¶105 (admitting that Bell does not disclose "the requirement that the anti-C5 antibody 'comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4"); ALXN2032, 146:17-25; ALXN2022 ¶204.) As Dr. Balthasar admitted, nothing in Bell disclosed or suggested to a POSA that "eculizumab" had a hybrid IgG2/G4 heavy chain constant region. (*See, e.g.*, ALXN2032, 151:4-12, 160:7-9; ALXN2022, ¶206.)

Rather, as the Board recognized, to the extent Bell disclosed anything about the structure of "eculizumab," it would have directed a POSA towards an antibody with an ***IgG4*** heavy chain constant region – as did Hillmen, Hill, and the many other references pointing to Thomas (AMG1023) for disclosure of "eculizumab". (*See* Paper No. 15, 21 n.14; ALXN2022, ¶¶204-207; *supra* Section II.C.)

Accordingly, a POSA reading Bell would have envisioned "eculizumab" to have a different structure and amino acid sequence from an antibody consisting of SEQ ID NOs: 2 and 4 as claimed in the '149 patent – which again, Amgen concedes was not disclosed anywhere in Bell. (ALXN2032, 146:17-25, 151:4-12.)

Specifically, Bell cited two documents – Thomas (AMG1023) and Evans (AMG1007) – for disclosing "[m]ethods for the preparation of h5G1.1-mAb, h5G1.1-scFv, and other functional fragments," and further identified "[t]he antibody h5G1.1-mAb" in this context as "eculizumab." (AMG1005 ¶[0052]; ALXN2032, 160:18-162:11.) As Dr. Casadevall's **Figure 9** illustrates, a POSA as of March 15, 2007 reading Bell would have understood that, between Thomas and Evans, only Thomas could have disclosed "eculizumab," because only Thomas disclosed an intact, full-length humanized "h5G1.1" antibody, while Evans disclosed humanized scFvs and other "fragments." (ALXN2022 ¶¶204-207; ALXN2032, 163:12-15, 163:25-164:5, 164:12-16; 169:13-18; *see supra* 44-47.)



2. A POSA Would Not Have Been Motivated to Combine Bell's Teachings with Bowdish and Evans, or to Make the Specific Claimed Sequence

For the same reason Amgen contends that Bell would have motivated a POSA to make the specific monoclonal antibody "eculizumab" – a C5-binding, clinically-tested antibody that Bell and other clinical literature consistently described as having an ***IgG4*** isotype – a POSA would ***not*** have been motivated to disregard Bell's teachings, and instead make a different antibody with the uniquely-engineered amino acid sequence recited in claim 1 of '149 patent.

A POSA would not have known of an antibody having the specific sequence claimed in the '149 patent – which differs from the IgG4 isotype antibody that Bell

identifies as "eculizumab" – and would not have been aware that an antibody with the claimed sequence had ever been tested *in vitro* or clinically. (ALXN2022, ¶¶135; *see supra* Section II.B.) In view of the unpredictability in the field of therapeutic antibody design, a POSA knowing of the clinically-proven anti-C5 antibody "eculizumab" would not have been motivated to make an antibody with a different, unstudied amino acid sequence – which might neither bind C5, nor be therapeutically useful or suitable for human administration. (ALXN2022, ¶¶209, 221-229.)

Amgen agrees, arguing in Ground 4 that a POSA as of March 15, 2007 reading Bell would have been specifically motivated to make "eculizumab," and not other, different antibodies. (Petition, 41, 45.) But then, Amgen disregards what Bell and other literature ***actually*** taught actually about "eculizumab" – that it was an IgG4 isotype antibody as described in Thomas. Instead, Amgen implausibly contends that a POSA seeking the sequence of "eculizumab" would have turned to ***Bowdish*** – a document that a POSA would have had no reason to associate with "eculizumab." (Petition, 45-47; AMG1002, ¶¶114-115; (ALXN2022, ¶¶209-213.) There is no reason why a POSA without the benefit of hindsight would have jumped from Bell to Bowdish for an understanding of "eculizumab," as Amgen contends. *See, e.g.*, *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019).

Amgen's hindsight-driven rationale for combining Bell (regarding the anti-C5 antibody "eculizumab") with Bowdish (regarding a TPO-mimetic fusion compound) falls apart under scrutiny, because it depends on assumptions that lack support or even expressly contradict the art's teachings. For example, Amgen asserts that Bowdish was a "known teaching[] in the art pertaining to eculizumab (5G1.1)." (Petition, 45.) But there is no dispute that Bell did ***not*** cite to Bowdish (for "eculizumab" or otherwise), and Bowdish itself made no mention of "eculizumab." (ALXN2022, ¶¶211-212; ALXN2032, 199:9-17.) Nor did any of the other publications cited by Amgen (*e.g.*, Hill, Hillmen, *etc.*) cite Bowdish for "eculizumab" or otherwise. Bowdish did not concern the development of anti-C5 antibodies at all, but rather focused on generating peptide-mimetic fusion compounds having nothing to do with C5 binding or treatment of PNH. (*See, e.g.*, AMG1006 ¶ [0006]; ALXN2022, ¶¶159-160, 211; ALXN2032, 174:2-12, 175:22-176:6, 180:8-11, 181:5-15.)

Dr. Balthasar's only stated "reason" for a POSA to "look to Bowdish" and "link" Bowdish to Bell further reveals his use of improper hindsight. (ALXN2022 ¶¶221-229.) Dr. Balthasar contends, a POSA would have connected Bell and Bowdish because (1) Bell's "eculizumab was . . . known to [*sic*] a humanized 5G1.1 with a hybrid IgG2/IgG4 constant region," and (2) "Bowdish . . . provides most of the sequence of humanized 5G1.1 with a hybrid IgG2/IgG4 constant

region." (AMG1002, ¶115; ALXN2032, 196:15-23, 197:15-25; Petition, 45.) That "reason" falls apart under scrutiny.

First, Amgen and Dr. Balthasar are wrong to suggest that Bowdish identified its TPO-mimetic compound as relating to "humanized 5G1.1" or "h5G1.1." (*See, e.g.*, Petition, 46 (claiming that Bowdish "explicitly direct[ed]" a POSA to look to Evans for "information" on the "h5G1.1 antibody" used to generate Bowdish's TPO-mimetic compound).) As Dr. Balthasar admitted, Bowdish used the term "5G1.1," not "h5G1.1" or "humanized 5G1.1"; and nothing in Bowdish said that the "scaffold" antibody used to generate its TPO-mimetic compound was a "humanized antibody." (ALXN2032, 199:19-23, 200:24-200:2; ALXN2022, ¶¶162, 164, 197-199, 216-217.) Rather, Bowdish references the '283 application (issued as Evans) for "[c]onstruction of 5G1.1" – a term that, , as discussed above, refers a ***mouse*** antibody when used in Evans. (*See supra* Section IV.B.1.) Even if a POSA did understand Bowdish to be referencing Evans for disclosure of an "h5G1.1 antibody" that was used as Bowdish's "scaffold," they would have found none, because Evans did not disclose ***any*** full length humanized antibodies derived from "5G1.1." (*See supra* 18-21.)

Second, Bell suggested that "eculizumab" had an ***IgG4*** constant region, and nothing in Bell pointed towards a hybrid IgG2/IgG4 constant region. (*See, e.g.*, AMG1002, ¶105; ALXN2032, 146:17-25, 151:4-12, 160:7-9.) Amgen's attempt

to associate "eculizumab" with a hybrid IgG2/IgG4 structure ignores Bell entirely, and instead relies on ***non-prior art*** information, and Mueller (AMG1008), which does not mention "eculizumab" at all. (ALXN2032, 55:5-57:1, 58:23-59:3, 59:23-60:6, 60:13-16, 61:13-62:4, 63:5-64:19.) For example, Amgen relies on out-of-context statements made in 2011 from the file history of U.S. App. No. 11/127,438 ("the '438 application") – which is not related to the '149 patent.[5] (*See, e.g.*, Petition, 12 (citing AMG1049, 838-39, 855).) These non-prior art statements cite ***nothing*** dated prior to March 15, 2007 identifying "eculizumab" as having a hybrid IgG2/IgG4 constant region. Instead, they cite Mueller II (AMG1031) – a document that makes no mention of "eculizumab," and merely identified "h5G1.1 HuG4" and "h5G1.1 HuG2/G4" as experimental controls – of which ***only*** the "HuG4" antibody was described as an "anti-C5 antibody." (AMG1031, 446; AMG1008, 12:1-2; ALXN2022, ¶166; ALXN2032, 242:21-243:14.) The prior art must be viewed "***without the benefit of the invention***" – and Amgen failed to do

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[5] Amgen and Dr. Balthasar also rely on a non-prior art publication from November 2007 (AMG1033), and a 2017 submission from an Alexion employee during prosecution of the '149 patent (AMG1015 at 734-741.) (AMG1002 ¶¶11, 54; ALXN2032, 55:5-57:1, 58:23-59:3, 63:5-64:1, 64:8-19.)

so by disregarding the overwhelming teaching by Bell and the other art that "eculizumab" was described as the IgG4 antibody of Thomas. *See Neptune Generics, LLC v. Eli Lilly & Co.*, IPR2016-00237, Paper 84 at 74-77 (Oct. 5, 2017), *aff'd*, 921 F.3d 1372 (Fed. Cir. 2019).

Third, Dr. Balthasar admits that nothing in Bowdish referred to its TPO-mimetic compound as having an "IgG2/IgG4" constant region structure. (ALXN2032, 212:22-213:2, 214:2-7.) Dr. Balthasar fails to prove his contention that a POSA would have identified the hybrid IgG2/IgG4 structure of Bowdish's TPO-mimetic compound using "BLAST or a similar search tool." (ALXN2032, 212:22-213:2, 214:2-7.) Bowdish itself did not guide a POSA to apply such "search tools" to its peptide-mimetic compounds. ([ALXN2022, ¶216; ALXN2032, 214:19-24.) Further, Amgen presents ***no evidence*** of "the search results that a POSA would have gotten if, prior to March 15, 2007, they had tried to evaluate the sequences in Bowdish Figures 13A and 13B using 'BLAST or a similar search tool.'" (ALXN2032, 214:25-215:8.)

A POSA also would not have connected Bell and Bowdish simply because Bowdish used the term "5G1.1." (ALXN2022, ¶219.) As Dr. Balthasar testified, a POSA would have understood that the term "5G1.1" alone was ***not*** limited to "eculizumab," and depending on the context, could refer to the original "5G1.1" hybridoma, the "5G1.1" mouse antibody from the hybridoma (as used in Evans), as

well as many possible "variants" of that antibody with different structures and sequences. (ALXN2032, 98:22-99:8, 100:16-24, 165:5-21; 169:6-18; 202:24-203:16; ALXN2022, ¶¶95-96.) In contrast, the term "eculizumab" as used in Bell referred to only one humanized monoclonal antibody, having a specific (but unknown) amino acid sequence. (*See supra* Section II.B.) A POSA looking for more information on "eculizumab" thus would have considered the art's pertinent teachings regarding "***eculizumab*" – *not*** the far broader term ***"5G1.1."*** (ALXN2022, ¶219.) And a POSA certainly would not have focused on Bowdish, which contained no data showing that its TPO-mimetic compound or its "scaffold" antibody would bind C5 or treat complement-mediated conditions such as PNH. (ALXN2022, ¶¶211, 228-229.)

Amgen's Ground 4 improperly uses the '149 patent as a ***reference point*** for reconstructing the amino acid sequence of the claimed antibody, from sequences selectively plucked and combined from Bowdish and Evans. (*See, e.g.*, AMG1002 Figs. 4-7, 13 (hindsight sequence comparisons between the '149 patent and select sequences from Bowdish or Evans), and Figs. 3, 10, 11 and 12 (using green coloration to signify sequences corresponding in hindsight to the '149 patent).) As Dr. Balthasar concedes, a POSA could not have made any of these comparisons, because a POSA would not have had access to the sequence of the '149 patent. (ALXN2032, 222:7-224:24.) Further, Amgen and Dr. Balthasar disclose ***only*** the

carefully-selected prior art sequences from Bowdish and Evans that they knew ***in hindsight*** would "align[] perfectly" with the '149 patent sequence that was not available to a POSA prior to March 15, 2007. (*See, e.g.*, AMG1002 ¶¶ 51, 53, 102.) But "working backwards from [a] compound, with the benefit of hindsight, once one is aware of it does not render it obvious." *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019).

For example, Amgen presented hindsight alignments between the '149 patent and portions of Evans SEQ ID NO: 20 – a humanized scFv compound (AMG1002, Figs. 6-7) – but withheld from the Board the many other disclosures in Evans that would ***not*** have aligned with the claimed sequence, including:

- Evans Figures 18 and 19 – the variable regions of the mouse antibody that Bowdish references (with respect to the '283 application) for "[c]onstruction of 5G1.1" (ALXN2022, ¶¶ 214-215; ALXN2032, 169:19-170:4);
- The "Fd" molecules of Evans SEQ ID NOs: 11, and 12, which a POSA would have understood were more "complete" fragments of a humanized antibody than an scFv, and provide sequences in the constant region (and for SEQ ID NO: 11, the variable region) that do not align with the '149 patent sequence (ALXN2022, ¶129); and

- The eight other humanized "scFv" molecules of Evans, which Dr. Balthasar admits were different from SEQ ID NO: 20 (*See* AMG1007, 43:6-14, 43:62-45:4; ALXN2022, ¶156; ALXN2032, 222:22-223:9.)

Even assuming the disclosures of Bowdish and Evans were fully combined, a POSA without hindsight would not have been directed to the complete amino acid sequence recited in claim 1 of the '149 patent. (*See supra* Section IV.B.2.)

Amgen further uses improper hindsight by ignoring the disclosure of variable region sequences in ***Thomas*** (AMG1023), which Bell cites alongside Evans. If, prior to March 15, 2007, a POSA reading Bell were to have followed its reference to Thomas for "eculizumab," they would have been directed to variable region sequences that would ***not*** "align perfectly" with the non-prior art '149 patent sequence. For example, all of the light chain regions disclosed for "5G1.1" and various mouse and humanized compounds derived from "5G1.1" disclosed in Thomas have an arginine ("R") at light chain position 38, whereas the claimed sequence of the '149 patent has a glutamine ("Gln"). (AMG1023, 1392, 1396; ALXN2022, ¶244.)

3. A POSA Without Hindsight Would Not Have Reasonably Expected <u>Success with the Combination of Bell, Bowdish and Evans</u>

Amgen's Ground 4 also fails to show that a POSA would have reasonably expected that the antibody it constructs in hindsight from Bowdish and Evans

would be an "[a]n antibody that binds C5," as claim 1 of the '149 patent requires. *See, e.g.*, *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1383 (Fed. Cir. 2019). Amgen relies exclusively on Bell for the teaching of this element. (Petition, 41-42; AMG1002, ¶114.) But Bell only identified "eculizumab" (citing to Thomas's IgG4 antibody) as an anti-C5 antibody, and taught nothing about the C5 binding, if any, of a different antibody with the specific amino acid sequence recited in claim 1 of the '149 patent. (*See supra* Sections IV.B.3, IV.C.1.) Likewise, as discussed above, Bowdish stated nothing regarding the C5 binding, if any, of its TPO-mimetic compound or the "scaffold" antibody it was made from. (*See supra* Section IV.B.2-3.) And as discussed above in Section IV.B.2-3, Evans did not disclose any C5 binding data for the claimed antibody of the '149 patent, or for any other full-length humanized antibody.

In the absence of any disclosure that the antibody with the sequence claimed in the '149 patent was "[a]n antibody that binds C5," a POSA would not have reasonably expected that antibody to bind C5. (ALXN2022, ¶¶ 221-229.)

D. Amgen's Ground 5 Fails Because Amgen Cannot Show that Claim 1 Would Have Been Obvious Over the Combination of Evans and Mueller

Amgen's Ground 5 contends that claim 1 of the '149 patent would have been obvious over a combination of Evans (AMG1007) and Mueller (AMG1008). As the Board correctly found, Amgen's Ground 5 fails, because it relies upon

Amgen's present-day knowledge of the antibody sequence recited in claim 1, which Amgen uses as a guide to pick and combine sequences that it knows in hindsight will align with it. Without the benefit of hindsight, a POSA as of March 15, 2007 would have ***no motivation*** to combine Evans with Mueller to obtain the claimed antibody of the '149 patent; would have had ***no reason*** to pick and combine the specific sequences that Amgen selects from Evans and Mueller to reconstruct the claimed antibody of the '149 patent; and would have ***no reasonable expectation*** that such a new untested antibody would be "[a]n antibody that binds C5," as claim 1 requires. . (ALXN2022, ¶¶ 230-252.)

Nothing in Evans, Mueller, or elsewhere in the art would have motivated a POSA prior to March 15, 2007 to combine the two documents to obtain the specific amino acid sequence claimed in the '149 patent. Mueller did not cite to Evans, and Evans did not cite to Mueller. (ALXN2022, ¶233; ALXN2032, 170:21-171:20, 243:16-20.) A POSA also would not have been motivated to consult Evans and Mueller simultaneously, because they addressed very different technological problems. *See, e.g.*, *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013). While Evans characterized and tested the complement-blocking activity of the anti-C5 mouse "5G1.1" antibody and certain derivative compounds, Mueller studied antibodies to the porcine "VCAM" protein for treating or diagnosing human rejection of transplanted animal tissue, and did

not include any experiments or data on C5 binding or blocking C5 cleavage. (AMG1008, 1:4-19, 7:21-28, 8:34-13:16; ALXN2022, ¶¶165, 233, 242.) Insofar as Mueller described two "h5G1.1" antibodies – "h5G1.1 CO12 HuG4" and "h5G1.1 CO12 HuG2/G4" – these were exclusively used as "controls" for Mueller's study of its anti-VCAM antibodies. (AMG1008, 12:27-30 ALXN2022, ¶ 233; ALXN2032, 232:6-16.)

Amgen is incorrect a POSA "would have readily understood" Mueller's "h5G1.1 CO12 HuG2/G4 mAb" to be "eculizumab." (Petition, 56; *see also* Petition, 52; AMG1002, ¶136.) Neither Evans nor Mueller mentioned "eculizumab." (ALXN2032, 102:10-14, 199:15-17; ALXN2022 ¶166.) And, contrary to Amgen's assertions, the "overwhelming evidence in the art" was that the C5-binding, clinically proven antibody "eculizumab" antibody was Thomas's ***IgG4*** isotype antibody. (*See supra* Section II.C.) Consistent with that teaching, Mueller identified ***only*** the "h5G1.1 CO12 HuG4" antibody as an "anti-C5" antibody. (AMG1008, 12:1-3; ALXN2022, ¶166; *see supra* 57-58.)

Further, as the Board recognized, Amgen fails to show how a POSA without hindsight would have been motivated to combine specifically-selected sequences from Evans and Mueller, in the specific manner required to get the specific amino acid sequence of the antibody claimed in the '149 patent. (*See* Paper No. 15, 52-54.)

Again, Amgen's figures illustrate its use of improper hindsight. For example, Amgen's Figure 16 mistakenly suggests that a POSA would have understood Mueller and Evans to have disclosed the same single antibody, with part of the sequence being provided in Evans, and part of the sequence being provided in Mueller. (Petition, 49, Fig. 16; AMG1002 ¶ 133.) But, as Dr. Balthasar admits, Mueller did ***not*** disclose the amino acid sequence of any full-length "h5G1.1" antibody. (ALXN2032, 232:17-21; ALXN2022, ¶167.) Nor did Evans provide a partial sequence for a full-length humanized antibody, as Amgen's Figure 16 suggests. Rather, a POSA would have seen that Evans disclosed only a full-length "mouse" antibody, and truncated compounds like scFvs and Fabs that were ***not*** fragmented off a full-length antibody, but rather were produced from the ground up using recombinant DNA technology. (ALXN2022, ¶237; *see supra* 18-21.)

Neither Mueller nor Evans provided any ***guidance*** on how to combine their various sequences. As with Ground 4, Amgen's Ground 5 uses its present-day knowledge of the '149 patent to justify its selection and combination of sequences, by showing carefully curated sequence alignments that Amgen knows in hindsight will match with claimed sequence. (AMG1002 Figs. 10, 15-16, 18; ALXN2022, ¶¶239-247.)

E. The Objective Indicia of Nonobviousness Support Validity

Objective indicia of nonobviousness, including commercial success, long-felt but unmet need, and industry praise, further support the validity of the claim 1 of the '149 patent. *See, e.g., LEO Pharm. Prods., Ltd. v. Rea,* 726 F.3d 1346, 1358 (Fed. Cir. 2013).

There is no question that SOLIRIS® (eculizumab) is the commercial embodiment of the '149 patent, and that the objective evidence regarding SOLIRIS® and its commercial and therapeutic success has a direct nexus to the '149 patent. The '149 patent claims the sole active ingredient in SOLIRIS®: the uniquely-engineered, non-naturally occurring antibody comprising SEQ ID NOs: 2 and 4, which is responsible for the remarkable clinical properties of SOLIRIS®, and consequently, its commercial success as a treatment for PNH, as well as the complement-mediated hemolytic condition aHUS, and the neurologic conditions myasthenia gravis and NMOSD. (ALXN2022, ¶¶255-258; ALXN2032, 262:2-19.) *See, e.g., Henny Penny,* 938 F.3d at 1332; *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392-93 (Fed. Cir. 1988).

SOLIRIS® is unquestionably a commercial success, having generated substantial sales in the relevant market. The annual net product sales for SOLIRIS® have grown consistently since launch, including total U.S. sales of

$1 billion over the past three years, continuing to grow to over $1.588 billion in 2018 (a 28.6% increase from 2017). (ALXN2056; ALXN2059-ALXN2073.)

The invention of the '149 patent, in its commercial embodiment of SOLIRIS®, also fulfilled a long-felt, unmet need for a safe and effective treatment for PNH, a rare and potentially fatal blood disease. (ALXN2022, ¶¶260-269.) *See, e.g., Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994, 997-998 (Fed. Cir. 2009). Before SOLIRIS®, PNH patients had to suffer with debilitating symptoms and life-threatening thrombosis, and were often dependent on frequent blood transfusions for survival. (AMG1047, 2559; AMG1012, 1234; ALXN2022, ¶¶263-264.) SOLIRIS® was the ***first*** FDA-approved treatment to reduce hemolysis in patients with PNH – improving patients' quality of life and reducing their transfusion dependency. (ALXN2022, ¶¶262-267.) While other researchers before March 15, 2007 were interested in developing anti-C5 antibodies for treating PNH and other untreated complement-mediated conditions, only the inventors of SOLIRIS® succeeded in doing so. (ALXN2022, ¶¶268-269**;** ALXN2032, 262:23-263:3, 263:23-264:13; AMG1039.)

SOLIRIS® has also received industry praise as the recipient of multiple Prix Galien awards (the industry's highest accolade for pharmaceutical research and development), including the Prix Galien USA 2008 Award for Best Biotechnology Product, and the Prix Galien France 2009 Award for Most Innovative Drug for Rare Disease. (ALXN2020; ALXN2021; ALXN2022, ¶¶273-274.)

The substantial efforts by Amgen and others to copy SOLIRIS® with their own proposed biosimilar eculizumab products – which would necessarily include the claimed antibody of the '149 patent – is further strong evidence of the nonobviousness of the '149 patent. (ALXN2088; ALXN2090; ALXN2089; (ALXN2022, ¶¶275-276.) That Amgen has chosen to copy the specific amino acid sequence of the '149 patent, rather than make different anti-C5 antibody with a different amino acid sequence, evidences the significant impact of the '149 patent's invention. *See Liqwd, Inc. v. L'Oreal USA, Inc.*, --- F.3d ---, 2019 WL 5587047, at *2 (Fed. Cir. Oct. 17, 2019).

V. CONCLUSION

Alexion respectfully submits that the Board confirm the patentability of claim 1.[6]

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[6] Alexion provides this Patent Owner Response without prejudice to its right to raise a further constitutional challenge on appeal, including but not limited to challenges to the Board's institution decision and final written decision, based on the Federal Circuit's resolution of pending challenges. *Arthrex, Inc. v. Smith & Nephew, Inc.*, 2019 WL 5616010, at *11 (Fed. Cir. Oct. 31, 2019).

Respectfully submitted,

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CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing **PATENT OWNER RESPONSE and EXHIBITS ALXN2022-ALXN2091** were served via electronic mail November 22, 2019, in their entirety on the following:

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CERTIFICATION OF WORD COUNT

The undersigned hereby certifies that the portions of the above-captioned **PATENT OWNER RESPONSE** specified in 37 C.F.R. § 42.24 has 13,562 words, in compliance with the 14,000 word limit set forth in 37 C.F.R. § 42.24. This word count was prepared using Microsoft Word.

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