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. IPR2019-00739
Patent: 9,725,504

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

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I. INTRODUCTION

Claims 1-10 of Alexion's U.S. Patent No. 9,725,504 ("the '504 patent") recite methods of treating a patient suffering from paroxysmal nocturnal hemoglobinuria ("PNH") with a pharmaceutical composition of an antibody comprising the novel, uniquely-engineered amino acid sequence of SOLIRIS®, the groundbreaking, commercially successful anti-C5 monoclonal antibody developed by Alexion. Claim 6 also specifically requires that the composition is a "300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution."

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 '504 patent, the unique amino acid sequence of SOLIRIS® recited in claims 1-10 of the '504 patent (heavy and light chains consisting of SEQ ID NOs: 2 and 4, respectively) 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, formulated, and clinically tested an antibody named "eculizumab," the POSA would not have known that "eculizumab" had the amino acid sequence recited in the '504 patent claims. 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 in the methods of treatment and pharmaceutical compositions of the '504 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 claims 1-10 of the '504 patent and would not have reasonably expected that such an antibody would bind C5. Further, a POSA prior to March 15, 2007 would not have known or reasonably expected that such a novel antibody – with no *in vitro* or *in vivo* biological data or formulation information reported in the literature – could be formulated into a pharmaceutical composition suitable for use in treating PNH.

Amgen has not shown how any of the prior art of its Grounds disclosed or would have led a POSA to a method of treating PNH with pharmaceutical compositions comprising an antibody with the uniquely-engineered amino acid sequence recited in claims 1-10 of the '504 patent. Instead, Amgen disregards the perspective of a POSA as of March 15, 2007, and impermissibly uses its ***hindsight***

knowledge of the '504 patent's novel, previously-undisclosed claimed sequence and pharmaceutical compositions to misstate the disclosures of the prior art, pick and choose from those misstated disclosures, and reconstruct the claimed invention using the '504 patent's teachings as a guide. The law forbids such use of hindsight. When that improper hindsight is removed, and the art is viewed from the proper perspective of a POSA, each of Amgen's Grounds fails.

Amgen's Ground 1 – alleging anticipation of claims 1-3 and 7-10 – fails because Amgen incorrectly presumes that a POSA would have understood that the clinical publication Hillmen (AMG1004) disclosed the claimed sequence of the '504 patent by using the name "eculizumab." But nothing within the four corners of Hillmen necessarily disclosed the present-day knowledge that eculizumab has the uniquely-engineered amino acid sequence described and claimed in the '504 patent. Rather, as the Board recognized, Hillmen identified "eculizumab" as the ***IgG4 antibody of Thomas***. (*See, e.g.*, Paper No. 15, 28-29 & n.16, 33-35.)

Amgen's Grounds 2 and 3 – alleging obviousness of claims 4-6 in view of Hillmen in further combination with Bell (AMG1005) (claims 4 and 5) or Bell and Wang (AMG1028) (claim 6) – are based on the same mistaken premise that Hillmen disclosed the specific amino acid sequence claimed in the '504 patent, and fail for at least the same reasons as Ground 1. *See Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014) (in obviousness, as in

anticipation, an alleged inherent element must be "***necessarily present*** in the prior art combination").[1] Bell and Wang, like Hillmen, did not disclose the '504 patent's specific claimed amino acid sequence, or any pharmaceutical compositions of an antibody having that sequence. And Amgen fails to explain why a POSA would have been motivated to make, or would have reasonably expected success with, the specific pharmaceutical compositions recited in claim 6 for an antibody that, as far as a POSA knew, might have never been made or tested for C5 binding, *in vitro* activity, therapeutic effect in treating PNH (as the claims require), or suitability for pharmaceutical formulation.

Amgen's Grounds 4-7, alleging obviousness of claims 1-10, fail because they rely on post-hoc knowledge of the '504 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

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

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 '504 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 Grounds 4 and 5 contend that a POSA would have started with Bell (AMG1005), for teaching "eculizumab" as a clinically studied anti-C5 antibody (and for claim 6, Wang (AMG1028) for teaching compositions of "eculizumab") – and then would have turned to Bowdish (AMG1006) and Evans (AMG1007) for the sequence of "eculizumab." But ***nothing*** in Bowdish and Evans suggested to a POSA that the claimed antibody was "eculizumab." Rather, Bell – like Hillmen – informed a POSA that "eculizumab" was Thomas's ***IgG4*** antibody. (Paper No. 15, 29 n.16; IPR2019-00741, Paper No. 15, 21 n.14.) Amgen cannot explain why a POSA would have ignored the unequivocal direction toward Thomas's IgG4 antibody and instead looked to (1) Bowdish, which was not cited in Bell and disclosed neither "eculizumab" nor any other humanized monoclonal antibody that binds C5; and (2) Evans, which did not describe ***any*** full-length humanized antibodies for binding C5 or treating PNH, let alone the antibody of the claimed treatment methods and pharmaceutical compositions of the

’504 patent. There is no support for Amgen’s hindsight-driven theory that a POSA trying to determine the structure of Bell’s “eculizumab” would have (1) selected Bowdish, rather than Thomas, as a starting point; (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 Bell’s and many other prior art references’ teachings of “eculizumab” as an ***IgG4*** isotype antibody.

Even if Bowdish and Evans were viewed in combination, a POSA without hindsight would not have arrived at the specific sequence in the claimed compositions of the ’504 patent. Rather, a POSA would have seen Bowdish and Evans pointing in different directions, with Bowdish referring to a mouse antibody in its reference to “[c]onstruction of 5G1.1” from the “’283 application”; and Evans disclosing only that mouse antibody plus humanized recombinant “fragment” compounds that could not have been used as the “scaffold” to make Bowdish’s full-length TPO-mimetic compound.

Amgen’s Grounds 6 and 7 start with the disclosure of “eculizumab” by Bell (or Bell and Wang for claim 6), and then use improper hindsight to recreate the claimed sequence of the ’504 patent from sequences plucked from Evans and Mueller (AMG1008). 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*** 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 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 '504 patent. As the Board recognized, nothing in Evans or Mueller instructed whether or how such a combination should be done, including "precisely those portions of Evans's and Mueller's constructs to create an antibody having exactly the sequences set forth in SEQ ID NOs: 2 and 4." (Paper No. 15, 54.)

Even if sequences from Evans and Bowdish or Mueller were combined in the specific and untaught way that Amgen proposes, the methods of treatment and pharmaceutical compositions recited in claims 1-10 of the '504 patent considered as a whole would still not have been obvious in view of the art asserted in Grounds 4-7. First, a POSA would not have reasonably expected that an antibody with the claimed sequence would be "an antibody that binds C5," as the claims require. Further, a POSA would not have been motivated to use, or reasonably expected success in using, an uncharacterized antibody with the claimed sequence for a

"method of treating a patient suffering from [PNH]," or for inclusion in a "pharmaceutical composition" suitable for such treatment, as claims 1-10 require.

And even if Amgen were correct, as it contends in Grounds 3, 5, and 7, that the "eculizumab" antibody of Bell (AMG1005) and Wang (AMG1028) had the uniquely-engineered sequence recited in the '504 patent claims, it would not have been obvious for a POSA to formulate that composition as "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution," as required by claim 6. Amgen relies on Bell and Wang for allegedly teaching that such a composition would be "sufficiently stable and active to be used as a drug" and would be useful for treating PNH. (*E.g.*, Petition, 42 n.21.) But as Dr. Trout explains, nothing in Bell or Wang disclosed such a composition, or would have motivated a POSA without hindsight to make or use it. In particular, Bell disclosed no composition details at all; and Wang's disclosure of a 30 mg/ml eculizumab solution passed through a nebulizer device would not have motivated a POSA to make the claimed 300 mg single use, 10 mg/ml antibody solution compositions, or have given a POSA a reasonable expectation that such compositions would be suitable for use in treating PNH patients.

II. BACKGROUND

A. Design of Humanized Monoclonal Antibodies, and Pharmaceutical Compositions of Such 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 ¶71; 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 ¶¶77, 79.) And a POSA would have understood that a humanized monoclonal antibody for therapeutic use – the subject matter of the methods of treatment and pharmaceutical compositions described and claimed in the '504 patent – was a humanized monoclonal antibody intended to bind its target and achieve a desired biological and therapeutic activity when administered to human patients, while maintaining sufficient safety to be suitable for human administration. (*See* ALXN2022 ¶¶77-83, 87-91; ALXN2032, 43:15-22, 46:20-48:2.)

A POSA would have understood that development of a "humanized" antibody intended for human therapeutic use was a complex and unpredictable art.

(ALXN2022 ¶¶77-91.) 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 binding properties and biological activity. (ALXN2022 ¶83.) To determine the suitability of a new humanized antibody as a therapeutic agent, additional extensive testing would need to be performed, including "pre-clinical" testing in animals; clinical testing of efficacy, immunogenicity, and overall safety; and pharmaceutical formulation work to determine whether a suitably stable composition could be safely and efficaciously administered to people. (ALXN2022 ¶¶87-91; ALXN2032, 46:20-48:2.)

A POSA 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 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. (ALXN202022 ¶¶63-64, 71, 117.) In particular, it was known that even small changes in an antibody's sequence could affect its critical properties. (ALXN2022 ¶¶105-118.)

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 ¶¶105-118.) 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 ¶107.) 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 ¶¶108-115.) 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 ¶114; 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. (ALXN2022 ¶¶87-89.) 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 ¶87.)

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 ¶¶92-94.) 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 ¶92; 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 ¶¶68, 93; 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 ¶¶94, 106-118.)

A POSA also understood that developing pharmaceutical compositions of antibodies was an unpredictable art. (ALXN2024 ¶¶41-56; AMG1029, 1, 5.) Antibody compositions (liquid compositions in particular) were at risk for degradation that could cause them to lose effect or even harm patients – and thus would need to be tested to determine suitability for human use. (ALXN2024, ¶¶42-53.)

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 ¶95.) 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 ¶¶95-104; ALXN2032, 98:2-99:8, 159:1-10, 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 ¶96; 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 ¶96; 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 ¶98.) 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 ¶¶101-102, 121; 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 ¶103.)

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 ¶¶119-124; 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 '504 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 claims 1-10 of the '504 patent. (ALXN2022 ¶¶121-124; ALXN2032, 97:7-21.) Specifically, the literature regarding the development of "eculizumab" consistently described "eculizumab" by referencing Thomas (AMG1023). (ALXN2022 ¶¶121-124, 140, 194-196; ALXN2032, 125:13-126:9, 128:20-129:10, 192:13-22, 160:18-162:12.) Thomas, in turn, details 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 ¶124; ALXN2032, 242:21-243:4.)

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***)

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of 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 ¶124; ALXN2032, 242:21-243:4.)

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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 '504 patent. In particular, the light chain variable region sequence provided by Thomas differs from SEQ ID NO: 4 of the '504 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).)

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 ¶¶121-124.)

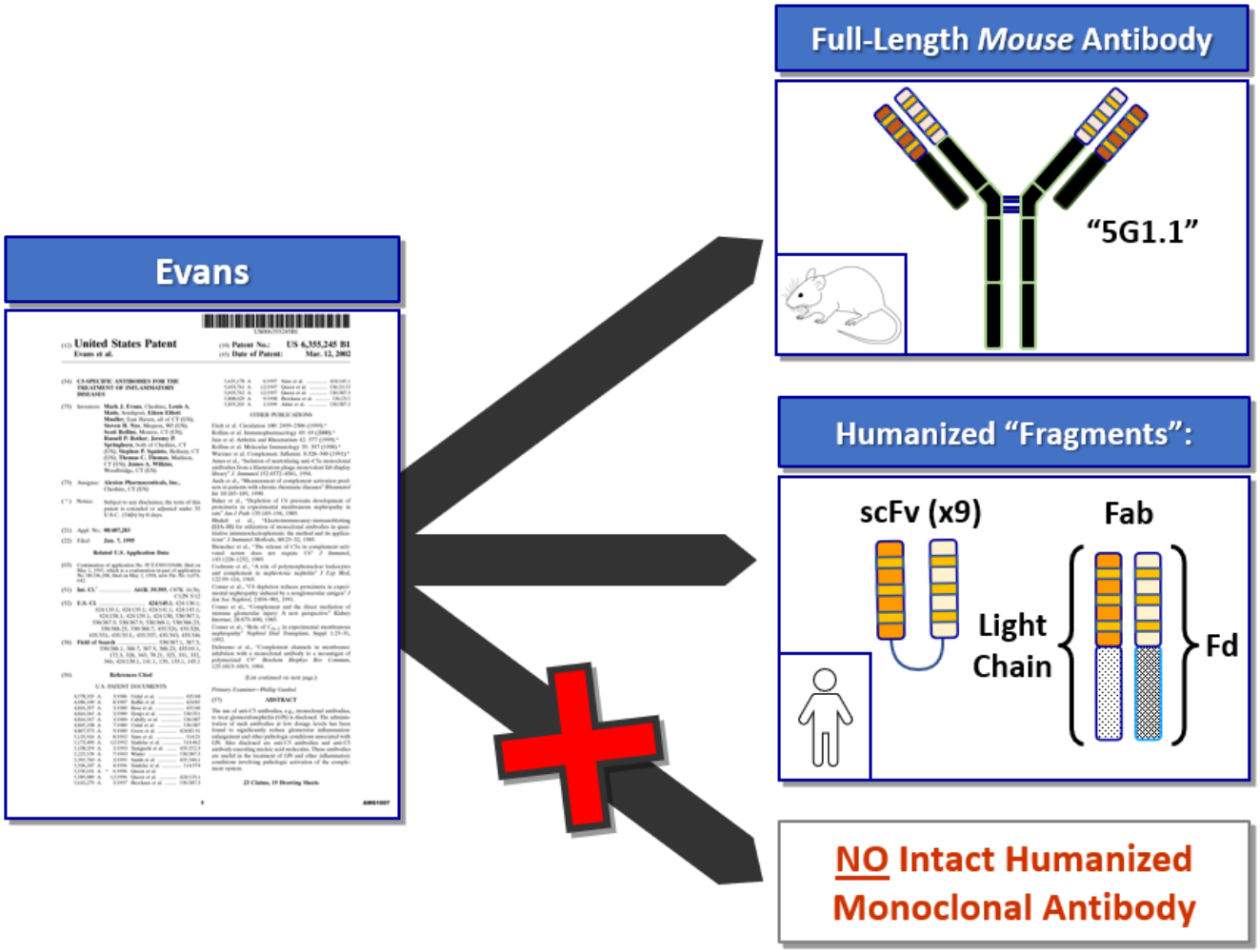
In contrast to Thomas and the literature regarding "eculizumab" that followed Thomas, a POSA would have understood that Evans (AMG1007) did ***not*** disclose "eculizumab." Rather, a POSA would have understood that Evans described an earlier stage of research that predated the design of the intact, full-length humanized antibody "eculizumab." (ALXN2022 ¶¶125-131.) It is undisputed that Evans did ***not*** disclose any full-length humanized antibodies. (ALXN2022 ¶¶125-129, 217, 223-224; 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 ¶¶126-129.) Evans further describes the researchers' characterization of the "5G1.1" mouse antibody, including its binding affinity, *in vitro* complement-blocking activity, and the

sequencing and cloning of the variable regions of the "5G1.1 mouse antibody." (AMG1007, Examples 7-10; ALXN2022 ¶126; 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 ¶127; 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 '504 patent. (AMG1007, Example 11; ALXN2022 ¶127.) 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 ¶127.) 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 '504 patent, including in "CH1" constant region. (ALXN2022 ¶130.) 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 '504 patent, it is known that SOLIRIS® has the specific amino acid sequence recited in claims 1-10 of the '504 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 '504 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, that it would be useful to treat patients suffering from PNH, or that it could be developed into a pharmaceutical composition suitable for human administration.

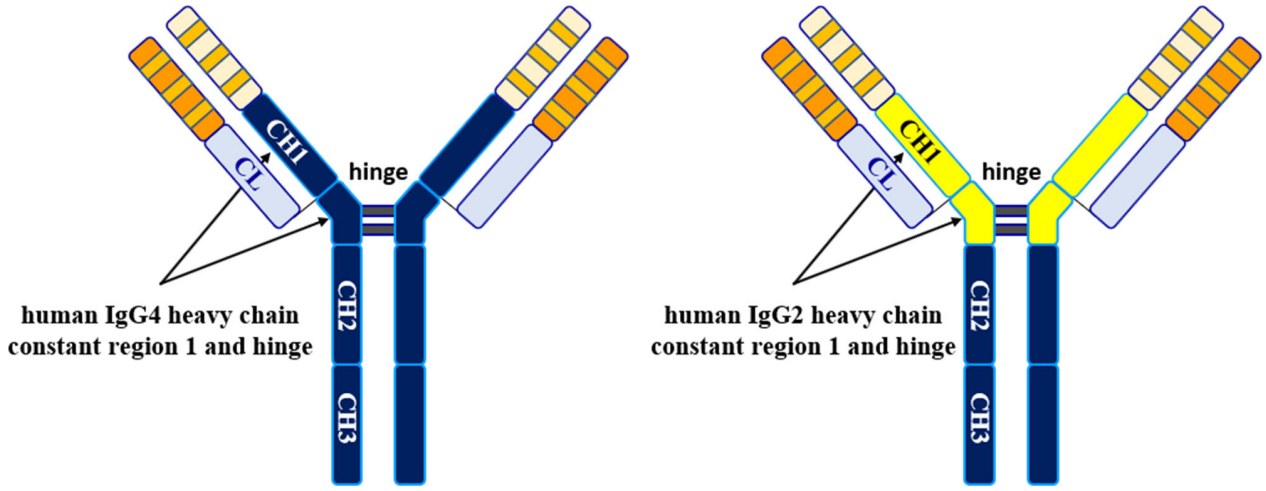
Today, but ***not*** prior to March 15, 2007, it is known that SOLIRIS® is a unique antibody that is ***very different*** from the humanized IgG4 antibody described in Thomas. As understood today, the heavy chain of SOLIRIS® (SEQ ID NO: 2) features a non-naturally occurring, uniquely-engineered constant region – containing sequences from both human IgG2 and IgG4 – that was designed by scientists at Alexion and was tested in human clinical trials. (ALXN2022 ¶¶134-137.)

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 claims 1-10 of the '504 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.

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, 16-17, 69-70; AMG1002, ¶¶43, 46, 56.) That 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 or 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

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[3] Notably, Amgen does not rely on Tacken (AMG1034) as the basis for any of its Grounds alleging anticipation or obviousness of the '504 patent.

such as PNH. (ALXN2022 ¶¶141-151; 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.)

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]

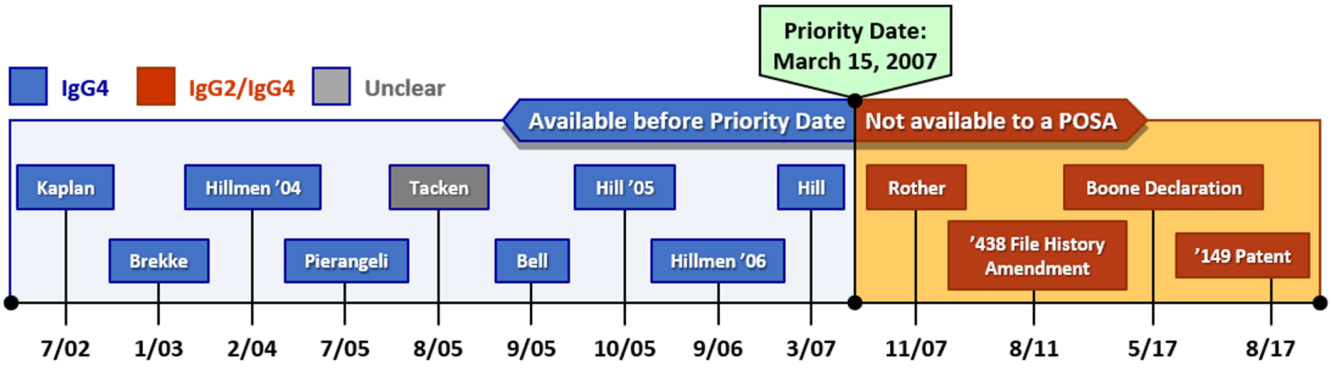
(AMG1034, 1279.) A POSA reading that isolated statement would not have been dissuaded from the consistent, clear teaching in the literature as of March 15, 2007 (both before and after Tacken's publication) identifying "eculizumab" and "SOLIRIS®" as the ***IgG4*** antibody of Thomas. (*See supra* Table 1; ALXN2022 ¶¶141-151.) 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 ¶144; 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. 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]; ALXN2022 ¶¶123, 146; 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); ALXN2022 ¶146; 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 content 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 ¶¶147, 151.) *See, e.g.*, *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 882-883 (Fed. Cir. 1998) (the "***entire content of the prior art***" must be considered in determining whether the art showed a trend towards the claimed invention).



E. Overview of the ’504 Patent

The ’504 patent issued on August 8, 2017 from U.S. App. No. 15/260,888, filed on September 9, 2016, and claims priority back to PCT/US2007/006606, filed on March 15, 2007. The ’504 patent has ten claims, all directed to methods of treating patients suffering from PNH with a composition of a uniquely-engineered anti-C5 antibody claimed by its amino acid sequence: “a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.” Claim 1 is the sole independent claim of the ’504 patent:

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

In addition to the elements of claim 1, claim 2 of the ’504 patent recites administration by “intravenous infusion”; claims 3 and 8 recite certain dosing amounts or regimens; and claim 7 additionally recites that “the patient is anemic.”

Claim 9 further provides that the treatment results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (“LDH”) – a biochemical marker of hemolysis in PNH patients; and claim 10 provides that the immediate decrease in LDH occurs within one week of administration.

Claims 4-6 of the ’504 patent also depend from claim 1, and recite additional elements specifying the claimed pharmaceutical composition. Claim 4 recites “a single unit dosage form,” which claim 5 provides is “a 300 mg single unit dosage form.” Claim 6 depends from claim 1, and recites “a 300 mg single-use formulation” that is “30 ml of a 10 mg/ml sterile, preservative free solution.”

The claims of the ’504 patent recite the complete amino acid sequence for SOLIRIS®: the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001, cols. 31-33, 35.) The ’504 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, 3:17-19, 19:51-28:45.) The ’504 patent also describes pharmaceutical compositions of eculizumab, including a “300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.” (AMG1001, 4:21-24, 5:21-25, 16:30-33.)

F. Prosecution History of the ’504 Patent and Related Applications

In prosecution leading to issuance of the ’504 patent, as well as the prosecution of related U.S. Patent Nos. 9,718,880 (“the ’880 patent”) and 9,732,149 (“the ’149 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. (AMG1014, 790.)

For example, in finding claims 1-10 of the '504 patent to be novel and nonobvious, the Examiner discussed Amgen's asserted references Hillmen (AMG1004), Evans (AMG1007), and Wang (AMG1028) as a basis for rejection before ultimately finding the claims to be allowable over the art. (*See, e.g.*, AMG1014, 557-561, 623-628, 738-743.) The Examiner also considered Amgen's asserted references Hill (AMG1047) and Bell (AMG1005); U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Bowdish (AMG1006); and Mueller II (AMG1031), which is cumulative of Mueller (AMG1008). (*See, e.g.*, AMG1014, 499, 565-566.) 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 in its Grounds: that Hillmen cites to ***Thomas*** (*i.e.*, "reference number 15" of Hillmen) as "disclosing more information about eculizumab." (AMG1014, 559, 623 (citing AMG1023).) Ultimately, the Examiner agreed that the prior art did not disclose or

suggest the specific claimed antibody sequence of the compositions recited in claims 1-10 of the '504 patent. (AMG1014, 790.)

The Examiner also credited the Declaration of Dr. Laural Boone (AMG1014, 763-770 ("the Boone Declaration") as showing that Alexion's clinical studies of the claimed antibody did not disclose its sequence or render it publicly accessible. (AMG1014, 790-91.) 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." (AMG1014, 767-770 ¶¶6-13; *id.*, 790.) While it is known ***today*** that SOLIRIS® as used in these studies had the claimed sequence of SEQ ID NOs: 2 and 4 (AMG1014, 767, ¶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 '504 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**"; that POSA would have had "skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics"; and that a POSA could work on a team with others having "specialized skills," including clinicians and formulation chemists. (Petition, 20-21.)

Alexion does not dispute Amgen's POSA definition, except to clarify – as the Board accepted (Paper No. 15, 19-21) – 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 ¶26.)

IV. AMGEN'S PETITION FAILS TO SHOW UNPATENTABILITY OF CLAIMS 1-10 OF THE '504 PATENT

A. Amgen's Ground 1 Fails Because Amgen Cannot Show that Claims 1-3 and 7-10 Were Anticipated by Hillmen

Amgen's Ground 1 contends that claims 1-3 and 7-10 of the '504 patent were anticipated by the clinical trial publication Hillmen (AMG1004). As the Board recognized, Amgen's Ground 1 fails because Amgen cannot show how Hillmen disclosed the antibody recited in claims 1-3 and 7-10 of the '504 patent.

1. Hillmen 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 Ground 1 fails because Hillmen did not expressly or inherently disclose all the elements recited in claims 1-3 and 7-10 of the '504 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.").

As the Board recognized, Hillmen fails to disclose an antibody comprising the specific amino acid sequence recited in claims 1-3 and 7-10 of the '504 patent. (Paper No. 15, 33-35.) Simply put, there were ***no amino acid sequences*** for

"eculizumab" disclosed anywhere within the four corners of the Hillmen publication. (ALXN2022 ¶¶176, 178-181.) And to the extent Hillmen provided any guidance about the structure of "eculizumab," it 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 '504 patent's SEQ ID NO: 2. (*See supra* Section II.C.) Dr. Balthasar conceded that Hillmen's statements regarding what "eculizumab is" cited to Thomas; and he was unable to identify ***any*** disclosure within Hillmen or its cited references suggesting that "eculizumab" had a hybrid IgG2/IgG4 constant region, rather than the IgG4 constant region of Thomas. (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.)

2. Hillmen Did Not Inherently Disclose the Unique, Non-Public Amino Acid Sequence of SOLIRIS® Recited in Claims 1-3 and 7-10 of the '504 Patent

To supply the claimed elements of SEQ ID NOs: 2 and 4 that are missing from Hillmen, 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. (Petition, 27, 30-32; ALXN2022 ¶¶182-183.)

For example, Amgen alleges inherent anticipation of claims 1-3 and 7-10 on the ground that ***today*** – years after the '504 patent's March 15, 2007 priority date – it is known that the clinical studies underlying Hillmen ***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, 27 (citing the May 11, 2017 Declaration of Dr. Laural Boone, AMG1014, 765, 7767).) But Amgen is mistaken on the law. The mere naming of an investigational product (*e.g.*, "eculizumab") in a 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 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 Grounds 2 and 3 Fail Because Amgen Cannot Show that Claims 4 and 5 Were Obvious Over Hillmen and Bell, or that Claim 6 Was Obvious Over Hillmen in Combination with Bell and Wang

Amgen's Grounds 2 and 3 contend that claims 4 and 5 of the '504 patent would have been obvious in view Hillmen and Bell (AMG1005), and Ground 3 contends that claim 6 would have been obvious over Hillmen in combination with Bell and Wang (AMG1028). As Grounds 2 and 3 raise overlapping issues, we address them together.

1. Hillmen and Bell (and Wang), in any Combination, Did Not Teach the Specific Claimed Antibody of Claims 4-6, or its Use in Treating Patients Suffering from PNH

Amgen's Grounds 2 and 3, like its Ground 1, rely upon Hillmen as allegedly disclosing the claimed amino acid sequence of claims 4-6 of the '504 patent. (*See* Petition, 25-31, 37, 41-42.) But nothing in Hillmen expressly or inherently disclosed that claimed sequence. (*See supra* Section IV.A.) As the Board agreed, Hillmen identified "eculizumab" as the ***IgG4*** isotype antibody of Thomas. (*See supra* Sections II.C, IV.A.) Likewise, Bell (AMG1005) and Wang (AMG1028) were silent on the sequence for "eculizumab." (*See, e.g.*, Petition, 45-47; ALXN2032, 146:17-25, 256:15-22.) And Bell, like Hillmen (which corresponds

to one of Bell's described studies), pointed to Thomas as a reference for "eculizumab."[4] (AMG1005, ¶[0052]; ALXN2022 ¶¶188, 196-199.)

Thus, nothing in Hillmen, Bell or Wang would have motivated a POSA to abandon Thomas's IgG4 antibody that they cite as "eculizumab," and instead attempt treating PNH using a different, unknown antibody with the sequence recited in the '504 patent, which was not disclosed anywhere in those documents. (ALXN2022 ¶¶187-190; *supra* Section IV.A.)

Nor would a POSA have reasonably expected success in using such an uncharacterized antibody in a "method of treating patients suffering from [PNH]," as an antibody's therapeutic effects or suitability for human administration could not have been reasonably predicted based on its amino acid sequence alone. (*See supra* Section II.A.) A POSA would have had no way to know, or even expect, that the then-undisclosed, uncharacterized antibody of the '504 patent would have therapeutic effect or be safe for administration. (ALXN2022 ¶¶189, 225-234.)

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[4] While Bell also cited Evans for the disclosure of antibody fragments, a POSA would have understood that Bell's regarding "eculizumab" to refer to Thomas, not Evans, because Evans did not disclose any full-length humanized antibodies. (*See, e.g.*, ALXN2022 ¶¶197-199, ALXN2032, 158:2-8, 159:14-160:3, 160:18-162:11, 163:5-15.)

2. The Claimed Pharmaceutical Compositions Were Not Taught by Hillmen and Bell (Claims 4 and 5) or Hillmen, Bell, and Wang (Claim 6)

With nothing in Hillmen and Bell (or Wang) disclosing an antibody with the specific sequence recited in claims 4-6 of the ’504 patent, a POSA would not have been motivated to make, or reasonably expected to succeed in making, a “pharmaceutical composition” of such an uncharacterized antibody, as claims 4-6 require. (ALXN2024, ¶¶64-91.) Nor would a POSA have been motivated to use any such compositions in a “method of treating a patient suffering from [PNH].” (ALXN2024 ¶¶64-91; ALXN2022 ¶¶190-191.)

As of March 15, 2007, antibody formulation was an empirical endeavor, and a POSA could not have reasonably expected that any particular uncharacterized antibody would be capable of development into any pharmaceutical composition suitable for human therapeutic use, or treatment of PNH in particular. (ALXN2024 ¶¶41-56, 71.) That concern would apply at both the commercial scale and the experimental scale, because a POSA would understand that pharmaceutical compositions needed to meet basic stability requirements to avoid harm to patients. (ALXN2024 ¶40.) A POSA particularly would have had no motivation, and no reasonable expectation of success, to formulate an uncharacterized antibody having a novel, hybrid “IgG2/IgG4” constant region

when nothing in the literature reported the formulation of such an antibody, on a commercial or experimental scale. (ALXN2024 ¶¶69-75.)

Nor would Bell or Wang have motivated a POSA to make the specific composition of claim 6 – "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution" – or have given a POSA a reasonable expectation of success in doing so. Bell described no specific pharmaceutical compositions, and only suggested that an undefined composition was used for purposes of administering "eculizumab" by intravenous infusion to treat PNH. (ALXN2024 ¶78; ALXN2022 ¶¶190-191.) A POSA without the benefit of hindsight would not have been motivated to combine Bell's teachings of an undefined composition ***for injection*** with Wang (AMG1028), which broadly concerned administration of a wide range of anti-C5 antibodies and fragments ***by inhalation through a "nebulizer"*** device for treating respiratory diseases. (AMG1028, ¶¶[0169]-[0173]; ALXN2024 ¶¶81-83; ALXN2032 257:24-258:15, 259:6-9.) *See, e.g.*, *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013).

Further, nothing in Wang disclosed a pharmaceutical composition containing a "10 mg/ml antibody solution" of "eculizumab" in a "single-use dosage form." (ALXN2024 ¶80.) Even if a POSA had associated Wang's "eculizumab" with the claimed antibody sequence – which Hillmen, Bell and Wang did ***not*** do – nothing

in Wang would have motivated a POSA to make such a composition of "eculizumab," or given a POSA a reasonable expectation of success in doing so. Wang did not specifically teach "eculizumab formulations of between 1 and 30 mg/ml" as Amgen claims (Petition, 41), but rather disclosed wide ranges including 1-30 mg/ml, 40-200 mg/ml and 1-200 mg/ml that hypothetically might be used ***for nebulization*** of various unrelated "anti-C5" antibodies and derivative compounds. (AMG1028, ¶¶[0067], [0130], [0170]-[0172], Fig. 10; ALXN2024 ¶¶84-86.)

Amgen's hindsight-driven combination of Bell and Wang is based on a misunderstanding of what Wang would have taught a POSA. According to Amgen, a POSA would have been motivated to make this combination, and arrive at the claimed 10 mg/ml concentration, because Wang allegedly taught that "eculizumab, formulated at a concentration of 1 to 30 mg/mL, would be ***sufficiently stable and active*** to be used as a drug." (Petition, 42 n.21; *see also* AMG1002 ¶113 ("[A] POSA would have arrived at a concentration of 10 mg/ml because Wang disclosed that eculizumab could be ***stably formulated*** at a concentration between 1 and 30 mg/ml, a range that encompasses 10 mg/ml.") But there is no such disclosure in Wang. Regarding stability, Wang only contained a highly general, hypothetical statement that compositions of undefined anti-C5 antibodies "may be stable" over a wide concentration range of 1-200 mg/ml

(AMG1028 ¶[0067]) – a statement that a POSA would ***not*** have taken as fact with respect to every specific antibody and concentration point. (ALXN2024 ¶86.)

A POSA would have understood that Wang's data, including the "SDS-PAGE" and "HPLC" studies of an unknown concentration of "eculizumab" that Amgen cites (Petition, 42 n.21), did ***not*** teach anything about stability pertinent to a pharmaceutical composition suitable for human administration, including for PNH. (ALXN2024 ¶¶87-88.) A POSA seeking a pharmaceutical composition of "eculizumab" for treatment of PNH would have been motivated to seek a composition with suitable stability under conditions pertinent to storage and transportation (*e.g.*, stability over time, and under different temperatures) to confirm that the product would not degrade prior to human administration to the point where it loses therapeutic effect or becomes dangerous to patients (*e.g.*, potentially immunogenic). (ALXN2024 ¶¶44-56, 84-88.); AMG1002 ¶107 ("Developing any given dosage form requires testing, validating, manufacturing, storing, and transporting that dosage form.") Wang disclosed no such data. Instead, Wang's studies of an "eculizumab" solution (at 30 mg/ml or an unspecified concentration) were limited to information irrelevant to the '504 patent, such as the formation of inhalable particles, and the "integrity of the nebulized antibody" when passed through various nebulizer mouthpieces – with ***no***

information on degradation over time or under storage conditions.[5] (AMG1028, ¶¶[0171]-[0173]; ALXN2024 ¶¶83-88.)

Bell and Wang also would not have motivated a POSA to make a "300 mg single-usage dosage form." Bell disclosed the administration of 600 mg and 900 mg dosages, but did not describe any particular dosage units or dosage forms. (ALXN2024 ¶91.) Amgen disregards the inconvenience of and greater possibility of provider error from having to use multiple 300 mg vials on each administration; and that antibody compositions were commonly available in multiple dosage forms of different strengths. (ALXN2024 ¶91.)

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[5] Amgen's reliance on other, unrelated antibodies commercially formulated at 10 mg/ml (Petition at 43, citing AMG1029, Table 1; AMG1030, Table 1) is misplaced, because (1) formulations of other antibodies could not reasonably be expected to work for "eculizumab"; (2) only ***one*** commercial product was a full-length humanized antibody in a 10 mg/ml solution; and (3) many commercial antibodies were not sufficiently stable to be formulated in solution in ***any*** concentration. (ALXN2024, ¶¶39-54, 88; AMG1029, 2-5.)

C. Amgen's Grounds 4 and 5 Fail Because Amgen Cannot Show that the '504 Patent Claims Would Have Been Obvious Over Bell, Bowdish and Evans (Claims 1-5, 7-10) or Bell, Wang, Bowdish and Evans (Claim 6)

Amgen's Ground 4 contends that claims 1-5 and 7-10 of the '504 patent would have been obvious over a combination of Bell (AMG1005), Bowdish (AMG1006) and Evans (AMG1007); and Amgen's Ground 5 contends that claim 6 would have been obvious over a combination of Bell, Wang (AMG1028), Bowdish and Evans. As Grounds 4 and 5 raise overlapping issues, we address them together.

Amgen's Grounds 4 and 5 fail because they are founded in an 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 and Evans, which make no mention of "eculizumab" or any other full-length humanized monoclonal antibodies known to bind C5 or have any therapeutic utility. (Petition, 45-54, 60-61.)

Without the benefit of hindsight, a POSA as of March 15, 2007 would have ***no reason*** to select and combine the sequences from Bowdish and Evans that Amgen cherry-picks to recreate the unique claimed sequences of the '504 patent; would have had ***no motivation*** to make, and treat PNH patients with, 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 suitable for a "method of treating a patient suffering from [PNH]," or suitable for formulation in a "pharmaceutical composition" for such treatment. (ALXN2022 ¶¶192-234; ALXN2024 ¶¶64-91.)

Even if Bowdish and Evans in combination disclosed amino acid sequences corresponding to SEQ ID NOs: 2 and 4 – which they did not – the combination of Bell, Bowdish and Evans did not motivate a POSA to use an uncharacterized antibody having that sequence in a "method of treating a patient suffering from [PNH]," or provide them with a reasonable expectation of success in doing so. There was no evidence that an antibody with SEQ ID NOs: 2 and 4 had ***ever*** been tested in people for therapeutic effect and tolerability, or even *in vitro* activity in binding C5 and blocking complement. *See, e.g.*, *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1383 (Fed. Cir. 2019) (finding no reasonable expectation of success for a method of treatment where "the asserted references do not disclose ***any*** data" regarding the effect of the claimed drug on the claimed disease) (emphasis in original). Nor would Bell, Bowdish, Evans, or Wang have taught a POSA to make pharmaceutical compositions of such an uncharacterized antibody – particularly with respect to the specific composition of claim 6.

The *Helsinn* decision cited by the Board (Paper No. 15, 46) confirms Amgen's failure to support Grounds 4-5 with any evidence prior to March 15,

2007 that the claimed antibody would be suitable for use in a pharmaceutical composition to treat PNH (as claim 1 requires), or any other condition. In *Helsinn*, the Court found that claims to pharmaceutical compositions for a clinical use ("reducing the likelihood of emesis") were ready for patenting even though Phase III clinical trials were not complete before the critical date, because there was "***overwhelming evidence . . . the patented invention would work for its intended purpose***," including full Phase II and preliminary Phase III clinical trial results for the claimed composition over a seven year period. *See Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, 855 F.3d 1356, 1372-1375 (Fed. Cir. 2017). With respect to the claimed methods of treatment and compositions of the '504 patent, however, a POSA would have seen no clinical studies, no formulation studies, no animal studies, no *in vitro* studies of complement-blocking activity, and no C5 binding studies. (*See supra* Section II.D.)

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

In Ground 4, Amgen relies on Bell (AMG1005) for its disclosure of "eculizumab" – which Bell identifies by name – as allegedly supplying every element of claims 1-5 and 7-10 of the '504 patent except the claimed amino acid sequence. (Petition, 45; AMG1002 ¶¶120, 130.) According to Amgen, a POSA would have specifically been motivated to make and use pharmaceutical

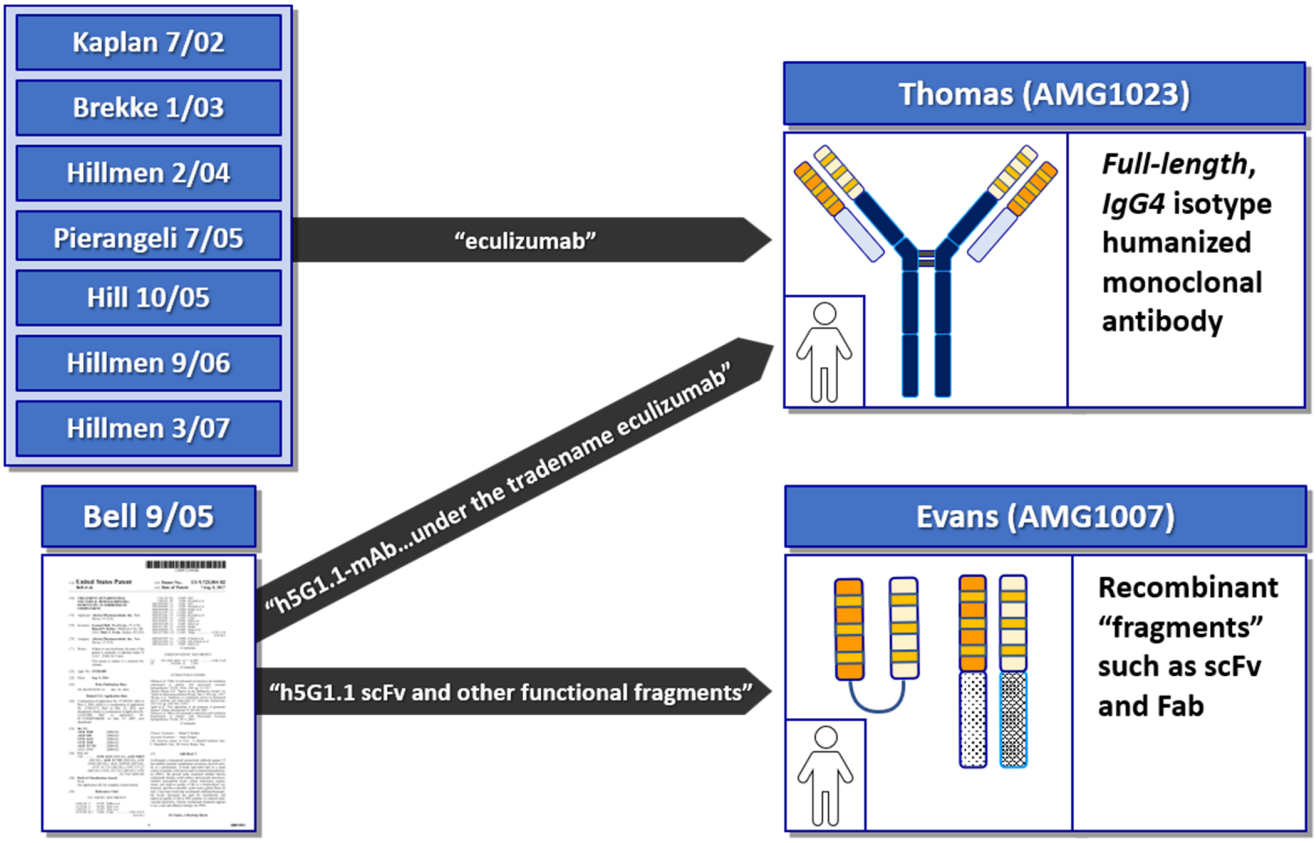
compositions of Bell's "eculizumab" antibody, in view of Bell's teaching that "eculizumab" binds C5, blocks its cleavage, and successfully treats PNH. (*See, e.g.*, AMG1002, ¶¶129-32; ALXN2032, 152:13-154: 7; ALXN2022 ¶¶196-196, 200.) For example, Dr. Balthasar admitted that Bell, along with Hillmen 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 – ***nothing*** in Bell (or Wang) disclosed the amino acid sequence for "eculizumab," or provided the specific amino acid sequence recited in claims 1-10 of the '504 patent. (Petition, 45-47; AMG1002, ¶130 (admitting that Bell did not disclose "the requirement that the 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, 257:13-18; ALXN2022 ¶¶194-197.) And, 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 ¶¶194-197, 204.)

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 and the many other references prior to March 15, 2007 pointing to Thomas (AMG1023) for disclosure

of "eculizumab." (ALXN2022 ¶¶119-124; *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 '504 patent – which again, Amgen concedes was not disclosed anywhere in Bell. (ALXN2022 ¶¶194-95.)

Specifically, paragraph [0052] of 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]; ALXN2022 ¶¶196-199; 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 scFvs and other "fragments." (ALXN2022 ¶¶196-199; ALXN2032, 163:5-15, 163:25-164:5, 164:12-16; 169:13-18; *see supra* 5-6, Section IV.B.1.)



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

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 of the methods claimed in the '504 patent.

A POSA would not have known of an antibody having the specific sequence claimed in the '504 patent – which differs from Thomas's 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 ¶¶152-153, 194-195, 207; *see supra* Section II.B.) In view of the unpredictability 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 ¶¶225-234.)

Amgen agrees, arguing in Ground 4 that POSA as of March 15, 2007 reading Bell would have been specifically motivated to make "eculizumab," and not other, different antibodies. (Petition, 45-47; AMG1002, ¶119-124; *see also* ALXN2032, 154:1-7.) 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." 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 as of March 15, 2007. For example, Amgen asserts that Bowdish was an "eculizumab teaching[] in the art." (Petition, 55.) But, like Hillmen and Hill, Bell did ***not*** cite to Bowdish (for "eculizumab" or otherwise), and Bowdish itself made no mention of "eculizumab." (ALXN2022 ¶¶200-203; ALXN2032, 170:5-10, 199:9-12.) 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 ¶¶161-162, 165, 202-203; 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 (AMG1002, ¶¶140, 169) further reveals his use of improper hindsight. (ALXN2022 ¶¶200-208.) As Dr. Balthasar contends, a POSA would have connected Bell and Bowdish because (1) Bell's "eculizumab was . . . known to be [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, ¶140; ALXN2032, 196:15-23, 197:15-25; *see also* Petition, 45-46.) 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." (ALXN32, 199:19-23, 200:24-200:2; ALXN2022 ¶¶165, 205, 223.) 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." **(**ALXN2032, 163:5-15**;** ALXN2022 ¶224.)

Second, Bell suggested that "eculizumab" had an ***IgG4*** constant region, and nothing in Bell pointed towards a hybrid IgG2/IgG4 constant region. (*See,* ALXN2032, 146:17-25, 151:3-12, 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 '504 patent.[6] (*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, 442-44; *see also* AMG1008, 11:36-12:32; ALXN2022 ¶¶167, 240; ALXN2032, 235:6-19, 237:8-15, 237:25-238:5, 238:13-19.) The prior art must be viewed "***without the***

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[6] 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 '504 patent (AMG1014, 763-770.) (*See* Petition at 13, 27, 38 n. 17, 50 n. 24; AMG1002, ¶¶11, 56; ALXN2032, 55:5-20, 56:24-57:1, 58:23-59:3, 64:8-14.)

benefit of the invention" – and Amgen failed to do so by disregarding the overwhelming teaching by Bell and the other art prior to March 15, 2007 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.) And 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 ¶205; 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 ¶207.) 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 ¶¶96-97.) 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 ¶207.) 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 ¶¶203, 233-234.)

Amgen's Grounds 4 and 5 improperly use the '504 patent as a ***reference point*** for reconstructing the uniquely-engineered amino acid sequence of the claimed antibody, from sequences selectively combined from Bowdish and Evans. (*See, e.g.*, AMG1002 Figs. 4-7, 13 (hindsight sequence comparisons between the '504 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 '504 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 ’504 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 ’504 patent sequence that was not available to a POSA prior to March 15, 2007. (*See, e.g.*, AMG1002, ¶¶52-53, 55, 80.) 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 ’504 patent and portions of Evans SEQ ID NO: 20 – a humanized scFv compound (AMG1002, ¶55) – 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 ¶¶215-216; 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'504 patent sequence (ALXN2022 ¶¶130, 159); and

- The eight other humanized "scFv" molecules of Evans, which Dr. Balthasar admits were different from SEQ ID NO: 20 (*see* AMG1007, 42:56-45:4; ALXN2022 ¶158; ALXN2032, 222:22-223:9)

Even if Bowdish and Evans were fully combined, a POSA would not have been directed to the complete amino acid sequence recited in claims 1-10 of the '504 patent. Among other things, a POSA would not have reasonably assumed that "heavy chain CDR3" referenced in Bowdish was the same as the heavy chain CDR3 described in Evans for humanized scFv compounds, which are ***not*** full-length structures like the TPO-mimetic compound of Evans. (ALXN2022 ¶¶217-221.) Even if a POSA reading Bowdish were to consider Evans for its disclosure of heavy chain CDR3 sequences, Evans allows for multiple options, and nothing in Bowdish or Evans indicates which, if any, were used in the "scaffold" antibody used to produce Bowdish's TPO-mimetic peptide. (AMG1006, [0005]-[0006], [0191]-[0192]; **[**ALXN2022 ¶¶217-221.)

Amgen further uses improper hindsight by ignoring the disclosure of variable region sequences in ***Thomas*** (AMG1023), which Bell cites alongside Evans. If 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 '504 patent sequence. (ALXN2022 ¶251.) 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 '504 patent has a glutamine ("Gln"). (AMG1023, 1392, 1396; ALXN2022 ¶251.)

3. The Combination of Bell, Bowdish and Evans (and Wang) Would Not Have Motivated a POSA to Practice the Claimed Treatment Methods and Pharmaceutical Compositions of the '504 Patent, or Given a POSA a Reasonable Expectation of Success in Doing So

Even if the claimed amino acid sequence of the '504 patent was disclosed by Bowdish and Evans – which Amgen has not shown – Amgen still cannot show that the claimed methods of treatment and pharmaceutical compositions of the '504 patent would have been obvious. First, nothing in Bowdish and Evans would have motivated a POSA to "treat[] a patient suffering from PNH" with the claimed antibody, or that the claimed antibody "binds C5." As discussed above, a POSA would not have understood Bowdish and Evans to disclose "eculizumab" or any full-length humanized anti-C5 antibody. (*See supra* Section IV.C.2.)

Second, nothing in Bowdish, Evans, or any other published literature report that an antibody having the claimed sequence of the '504 patent had been clinically tested. (ALXN2022 ¶¶134-135.) The only antibody identified in the pre-March

15, 2007 literature as having been tested in clinical trials for safety and efficacy in treating PNH, was the ***IgG4*** antibody of Thomas. (*See supra* Section II.C.) With no binding data, *in vitro* or animal testing, or clinical testing of the claimed antibody that Amgen assembles in hindsight from Bowdish and Evans, a POSA would have had no motivation to use that antibody in the claimed methods of treating PNH or pharmaceutical compositions for that use. (ALXN2022 ¶¶78-91, 134-137.) *See, e.g.*, *Endo*, 894 F.3d at 1380. And given the unpredictability of humanized monoclonal antibody design and development, a POSA would have had no reasonable expectation of success in practicing the claimed methods of treating patients suffering from PNH. (ALXN2022 ¶¶78-91, 134-137, 227-228, 257-259.) *OSI Pharms.*, 939 F.3d at 1383.

A POSA also would not have been motivated to make a "IgG2/IgG4" isotype – which Bowdish and Evans did not disclose – based on references that Amgen cites regarding purported benefits of that hybrid (*e.g.*, reduced immunogenicity). (Petition, 17, 52-54.) A POSA "would not have turned to a [hybrid isotype] approach to solve an undefined problem," when a POSA would have seen clinical literature pointing Thomas's IgG4 antibody as safe and effective to treat PNH, and understood the purported benefits of IgG2/IgG4 hybrids to be speculative and clinically untested. (ALXN2022 ¶¶78-91, 134-137, 227-228, 242, 257-258.) *See Amerigen Pharms.*, 913 F.3d at 1087.

Nor would Bowdish, Evans, Bell and Wang have motivated a POSA to make any pharmaceutical composition of the claimed antibody for use in treating patients suffering from PNH. A POSA would not have reasonably expected that an uncharacterized antibody would be suitable for formulation at all – particularly if it were thought to have a new hybrid isotype like IgG2/G4. (ALXN2024 ¶¶68-75; *see supra* Section IV.B.2.) Nothing in Bowdish, Evans, Bell or Wang would have motivated a POSA to make the specific claimed composition of claim 6: a "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution." (ALXN2044 ¶¶76-91; *see supra* Section IV.B.2.)

D. Amgen's Grounds 6 and 7 Fail Because Amgen Cannot Show that the '504 Patent Claims Would Have Been Obvious Over the Combination of Bell, Mueller and Evans (Claims 1-5, 7-10) or Bell, Wang, Mueller and Evans (Claim 6)

Amgen's Ground 6 contends that claims 1-5 and 7-10 of the '504 patent would have been obvious over a combination of Bell (AMG1005), Mueller (AMG1008) and Evans (AMG1007); and Amgen's Ground 7 contends that claim 6 would have been obvious over a combination of Bell, Wang (AMG1028), Mueller and Evans. As Grounds 6 and 7 raise overlapping issues and both Grounds fail for at least the same reasons, we address both Grounds together.

As the Board found, Amgen's Grounds 6 and 7 fail, because they rely upon Amgen's present-day knowledge of the antibody sequence recited in claims 1-10 of the '504 patent, which Amgen uses as a guide to pick and combine sequences

that it knows in hindsight will align it. Without the benefit of hindsight, a POSA would have had ***no motivation*** to combine Evans with Mueller to obtain the claimed antibody of the '504 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 '504 patent; and would have had ***no reasonable expectation*** that such a new untested antibody would be suitable for a "method of treating a patient suffering from [PNH]," or for formulation in a pharmaceutical composition for such treatment, as claims 1-10 all require. (ALXN2022 ¶¶235-261.) As stated above, even if Amgen's combination of Evans and Mueller were made, a POSA would not have been motivated to practice, or reasonably expected success in practicing, the specific method of treating PNH and pharmaceutical compositions of the '504 patent. (*See supra* Section II.A.)

As with Ground 4, Amgen's Ground 6 relies on Bell (AMG1005) for its disclosure of "eculizumab," as allegedly supplying every element of claims 1-5 and 7-10 except the claimed amino acid sequence. (Petition, 62; AMG1002 ¶¶172, 176.) As stated above, Bell and the overwhelming weight of the other art would have directed a POSA towards the IgG4 antibody of Thomas. (*See supra* Section II.C.)

Amgen cannot explain why a POSA would have leapt from Bell to Mueller, which Bell does not cite. Amgen states that a POSA would have been motivated to

do so by Mueller's teachings regarding whether its hybrid "G2/G4" constant regions would "activate the complement system." (Petition, 64.) But a POSA would have understood Thomas's antibody, cited for "eculizumab," to have been proven safe and effective in Phase II and Phase III clinical trials for treatment of PNH. (ALXN2022 ¶¶122-124.) A POSA with the proven clinical evidence pointing towards Thomas's antibody would have had no motivation to change it. *See Amerigen Pharms.*, 913 F.3d at 1087.

A POSA also would not have combined Bell and Mueller simply because they both reference "h5G1.1" – a broad term that could potentially refer to a number of different antibody structures. (ALXN2032, 98:2-99:8, 159:1-10, 202:24-203:14.) The only full-length "h5G1.1" antibody referenced in Bell is the IgG4 isotype antibody of Thomas that Bell cites as describing "eculizumab." (*See supra* 48-49.)

Nor would a POSA have been motivated to combine Evans with Mueller, when neither document cited to the other (Paper No. 15, 57; ALXN2022 ¶240; ALXN2032 170:21-171:20, 243:16-20), and they addressed very different technological problems. *See, e.g.*, *Broadcom*, 732 F.3d at 1334. 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 ¶¶167, 240.) 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 ¶240; 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, 69-70; *see also* Petition, 66; AMG1002, ¶179.) Neither Evans nor Mueller mentioned "eculizumab." (ALXN2032, 199:15-17, 102:10-14; ALXN2022 ¶168.) 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 ¶168; *see supra* 55-56, 64.)

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 claimed in the '504 patent. (*See* Paper No. 15, 52-54.) Amgen's figures illustrate its use of improper hindsight. For example, Amgen's Figure 14

mistakenly suggests that a POSA would have understood that Mueller and Evans disclosed the same single antibody, with part of the sequence being provided in Evans, and part of the sequence being provided in Mueller. (Petition, 63, Fig. 14; AMG1002, ¶173.) But, as Dr. Balthasar admits, Mueller did ***not*** disclose the amino acid sequences of any full-length "h5G1.1" antibodies. (ALXN2032, 232:17-21; ALXN2022 ¶169.) 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 scratch using recombinant DNA technology. (ALXN2022 ¶244; *see supra* 20-23.)

Neither Mueller nor Evans provided any ***guidance*** on how to combine their various sequences. As with Grounds 4 and 5, Amgen's Ground 6 and 7 use Amgen's present-day knowledge of the '504 patent to justify its selection and combination of sequences, by showing carefully curated sequence alignments that Amgen knows in hindsight will match with the claimed sequence. (AMG1002 Figs. 10, 14-16; ALXN2022 ¶¶246-254.)

Even if a POSA were to have combined sequences from Evans and Mueller in the exact way that Amgen does to reconstruct the claimed antibody, a POSA would not have (1) reasonably expected that the claimed antibody could be used

for "treating a patient suffering from [PNH]" or would even be "bind C5" (claims 1-10); (2) been motivated to make, or reasonably expected to succeed in making, a "pharmaceutical composition" of the claimed antibody for use in the claimed methods of treating PNH (claims 1-10); or (3) been motivated to make, or reasonably expected to succeed in making, a "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution" using the claimed antibody (claim 6). (*See supra* Section IV.B.2.)

As Dr. Balthasar conceded, nothing in Mueller disclosed that its "h5G1.1 CO12 HuG2/G4" antibody binds to C5; and nothing in Evans disclosed the binding properties of any full-length humanized antibodies, let alone one with a hybrid "IgG2/IgG4" constant region (which Evans also does not disclose). (ALXN2032, 247:13-18, 163:12-15; 163:25-164:5; 169:6-170:4; (ALXN2022 ¶¶156-157.) Further, Mueller contained no data providing any information on the efficacy or even safety of its "HuG2/G4" isotype control antibody, or suggested that it was ever formulated into a pharmaceutical composition. (ALXN2032, 247:20-248:6; ALXN2022 ¶¶255-262.) With such an uncharacterized antibody, a POSA would have had no motivation or reasonable expectation of success in using it to treat PNH patients, or to include it in any pharmaceutical formulation suitable for administration. (*See supra* Section II.A.) Nor would Bell or Wang have motivated

a POSA to make the specific claimed composition of claim 6: "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution." (*See supra* Section IV.B.2.)

E. <u>The Objective Indicia of Nonobviousness Support Validity</u>

Objective indicia of nonobviousness, including commercial success, long-felt but unmet need, and industry praise, further support the validity of the claims 1-10 of the '504 patent.

There is no question that SOLIRIS® (eculizumab) is the commercial embodiment of the '504 patent, and that the objective evidence regarding SOLIRIS® and its commercial and therapeutic success has a direct nexus to the '504 patent. The '504 patent claims "[a] method of treating a patient suffering from [PNH]" that corresponds to the groundbreaking SOLIRIS® indication for "[t]he treatment of patients with [PNH] to reduce hemolysis." (ALXN2053, 1; ALXN2022 ¶267.) Further, the '504 patent claims recite pharmaceutical compositions of 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. (ALXN2022 ¶¶265-268; 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).

Claim 6 claims the pharmaceutical composition of SOLIRIS®, which is supplied as a 300 mg single-dose vial containing 30 mg of a 10 mg/ml solution of the claimed antibody. (ALXN2053, 1; ALXN2022 ¶267.)

SOLIRIS® is unquestionably a huge commercial success. 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 ’504 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 ¶¶270-279.) *See 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 ¶¶273-274.) SOLIRIS® was the ***first*** FDA-approved treatment to reduce hemolysis in patients with PNH – transforming patients’ quality of life and reducing their transfusion dependency. (ALXN2022 ¶¶275-277.) While other researchers 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 ¶¶278-279; 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 ¶¶283-284.)

The substantial efforts by Amgen and other companies to copy SOLIRIS® with its their proposed biosimilar eculizumab products – which would necessarily include the claimed antibody of the '504 patent – is further strong evidence of the nonobviousness of the '504 patent. (ALXN2088; ALXN2090; ALXN2089; ALXN2022 ¶¶285-286.) That Amgen and at least three others have chosen to copy the specific amino acid sequence of the '504 patent, rather than make a different anti-C5 antibody with a different amino acid sequence, evidences the significant impact of the '504 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[7]

Alexion respectfully submits that the Board confirm the patentability of claims 1-10.

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[7] 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,

KING & SPALDING LLP

/Gerald J. Flattmann, Jr./

Gerald J. Flattmann, Jr. (Reg. No. 37,324)
Attorneys for Patent Owner, Alexion Pharmaceuticals, Inc.

Date: November 22, 2019
1185 Avenue of the Americas
New York, NY 10036
(212) 556-2157

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:

Deborah Sterling (Reg. No. 62,732)
David H. Holman (Reg. No. 61,205)
Scott A. Schaller (Reg. No. 60,167)
David W. Roadcap (Reg. No. 68,956)
STERNE KESSLER GOLDSTEIN & FOX PLLC
1100 New York Avenue NW
Washington, DC 20005
Tel: (202) 371-2600
dsterling-PTAB@sternekessler.com
dholman-PTAB@sternekessler.com
sschalle-PTAB@sternekessler.com
droadcap-PTAB@sternekessler.com

KING & SPALDING LLP

/Gerald J. Flattmann, Jr./

Gerald J. Flattmann, Jr. (Reg. No. 37,324)
Attorneys for Patent Owner, Alexion Pharmaceuticals, Inc.

Date: November 22, 2019
1185 Avenue of the Americas
New York, NY 10036
(212) 556-2157

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 13,746 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.

KING & SPALDING LLP

/Gerald J. Flattmann, Jr./

Gerald J. Flattmann, Jr. (Reg. No. 37,324)
Attorneys for Patent Owner, Alexion Pharmaceuticals, Inc.

Date: November 22, 2019
1185 Avenue of the Americas
New York, NY 10036
(212) 556-2157