

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2023-00999
Patent: 9,725,504

**PATENT OWNER'S RESPONSE
UNDER 37 C.F.R § 42.120**

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EXHIBIT LIST¹

Exhibit No.	Description of Document
2000 to 2004	<i>Intentionally left blank</i>
2005	SOLIRIS [®] Label
2006	Dmytrijuk et al., FDA Report: Eculizumab (SOLIRIS [®]) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria, THE ONCOLOGIST, 13:993 -1000 (2008)
2007	Janeway and Travers, <i>Immunobiology: The Immune System in Health and Disease</i> (Garland Science, 6thed. (2005))
2008	McCloskey <i>et al.</i> , Human Constant Regions Influence the Antibody Binding Characteristics of Mouse-Human Chimeric IgG Subclasses, IMMUNOLOGY, 88: 169-173 (1996)
2009	Torres <i>et al.</i> , The Immunoglobulin Heavy Chain Constant Region Affects Kinetic and Thermodynamic Parameters of Antibody Variable Region Interactions with Antigen, J. OF BIOL. CHEM., 282(18): 13917–27 (2007)
2010	Janda <i>et al.</i> , Ig Constant Region Effects on Variable Region Structure and Function, FRONT. MICROBIOL., 7(22): 1-10 (2016)

¹ Due to the similarities discussed below, Patent Owner is using many of the same exhibits, and thus the same exhibit numbers, here as used in the 2019 IPRs filed by Amgen so that the records remain consistent. Unused exhibits were removed and their exhibit numbers “intentionally left blank” and “reserved.” New exhibits were added to the end with new exhibit numbers.

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2019	Ricklin & Lambris, Complement-Targeted Therapeutics, NATURE BIOTECHNOLOGY, 25(11); 1265-1275 (2007)
2020	Alexion Press Release, Alexion's Soliris® Receives 2008 Prix Galien USA Award for Best Biotechnology Product, September 25, 2008, available at https://news.alexion.com/press-release/company-news/alexions-soliris-receives-2008-prix-galien-usa-award-best-biotechnology-p (last visited May 15, 2019)

2021	BusinessWire, Alexion's Soliris® Receives 2009 Prix Galien France for Most Innovative Drug for Rare Disease, June 10, 2009, available at https://www.businesswire.com/news/home/20090610005826/en/Alexions-Soliris®-Receives-2009-Prix-Galien-France (last visited May 15, 2019)
2022	Declaration of Arturo Casadevall, M.D., Ph.D. in IPR2019-00739
2023	Curriculum Vitae of Arturo Casadevall, M.D., Ph.D. in IPR2019-00739
2024	Declaration of Bernhardt L. Trout, Ph.D. in IPR2019-00739
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2047	McClean, et al., A point mutation in the CH3 domain of human IgG3 inhibits antibody secretion without affecting antigen specificity, MOLECULAR IMMUNOLOGY, 2005
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2049	HemOnc Today, Eculizumab's triumph over PNH, https://www.healio.com/hematology-oncology/news/print/hemonc-today/%7B01f97d7b-36b4-4462-aab4-02918370caa1%7D/eculizumabs-triumph-over-pnh (Aug. 25, 2008)
2050	Fatimah Al-Ani et al., "Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations, Ther. Clin. Risk Manag., 12:1161-1170 (2016)
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2053	June 2019 Soliris [®] Label
2054	Alexion Press Release, "Alexion Pharmaceuticals Submits Biologics License Application for Soliris [™] (eculizumab)," (Sept. 20, 2006)
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2104	Deposition Transcript of Jeffrey V. Ravetch, M.D., Ph.D. (Feb. 23, 2024)
2105	Declaration of Arturo Casadevall, M.D., Ph.D., 2024
2106	Deposition Transcript of Cindy Ippoliti, Pharm.D. (Feb. 20, 2024)

2107	Declaration of Bernhardt L. Trout, Ph.D., 2024
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I. INTRODUCTION

Claims 1-10 of the 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. 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 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.

Before 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 was not publicly known or disclosed in the prior art. While a person of ordinary skill in the art (“POSA”) as of that date would have known that Alexion had designed and clinically tested an antibody named “eculizumab,” the POSA would not have known that “eculizumab” had the uniquely-engineered amino acid sequence

claimed in the '504 patent. If a POSA were motivated to seek out the specific amino acid sequence of an antibody called “eculizumab,” then a POSA at that time would not be led to the sequence claimed in the '504 patent. Instead, because the literature as of March 15, 2007 consistently identified “eculizumab” as the antibody described in the “Thomas” publication (EX1010), a POSA would have been led to the antibody described in Thomas, which has a naturally-occurring “***IgG4***” heavy chain constant region.² In contrast, the novel antibody in the methods of the '504 patent has a uniquely-engineered, non-naturally occurring IgG2/G4 constant region.

Even if a POSA were to ignore Thomas, Samsung has not explained or shown how a POSA would have a reasonable expectation of success of choosing the exact sequences and arranging them exactly as disclosed by SEQ ID NOs: 2 and 4, and still retain anti-C5 activity as claimed. Samsung and this Panel disregard the perspective of a POSA as of March 15, 2007, and impermissibly use ***hindsight knowledge*** of the '504 patent's novel, previously-undisclosed claimed sequence to overstate the disclosures of the prior art, pick and choose from those

² Unless otherwise noted, all emphasis is added, and all internal citations and quotation marks are omitted.

misstated disclosures, and reconstruct the claimed invention using post-priority date information as a guide.

Namely, the patent, which fully discloses SEQ ID NOs: 2 and 4 as “eculizumab,” does not expressly state that SEQ ID NO: 2 is an IgG2/G4 heavy chain sequence. (*cf.* EX1001, 4:35-37 (stating “certain embodiments” can have an “altered” “G2/G4 construct”).) The knowledge that SEQ ID NO: 2 encodes a hybrid heavy chain originates from the prosecution history, which necessarily occurred after the March 15, 2007 priority date. Thus, Dr. Ravetch and this Panel both “reverse engineer[.]” (Paper No. 9, 31) the non-natural hybrid sequence from fragments of the prior art using post-priority date information as the guiding beacon. But, the prior art is ambiguous as to what “eculizumab” is. When the art is viewed from the proper perspective, a POSA would not have been certain what the sequence of “eculizumab” was, and more likely, would have been led to a wholly different antibody than the one claimed.

As previously demonstrated in the Declaration of Dr. Arturo Casadevall, submitted in IPR2019-00739³ (*see, e.g.*, ALXN2022, ¶¶ 139-173, 192-262), the arguments in Samsung's Petition amount to little more than a post-hoc narrative that reconstructs the claimed sequences piecemeal and in hindsight. A POSA would not have combined the art to arrive at those sequences on one's own back in 2007 and would have had no reasonable expectation that they would work as they do.

In instituting, the Board contradicted its earlier opinions concerning the Bell and Mueller references in the Amgen IPRs. It also misapplied the law of inherent anticipation and adopted wholesale Samsung's hindsight-driven, reverse-engineering of the claimed sequence from disparate portions of the prior art without a single acknowledgment of the countervailing evidence presented in the

³ The Casadevall Declaration (ALXN2022) was submitted in IPR2019-00739 in support of Alexion's Response. Although responsive to Amgen's Petition and expert declaration, the arguments contained in that Petition and declaration were substantially similar to those made here by Samsung and Dr. Ravetch. Therefore, Alexion cites to it for support here. In a new declaration, Dr. Casadevall has reaffirmed his opinions and authorized their use here. (ALXN2105.)

Casadevall Declaration. The latter is in particular an incorrect approach given it was Samsung's burden to show a reasonable likelihood of prevailing. When the law and facts are correctly applied, there is no reasonable likelihood that Samsung's Grounds will prevail.

Samsung's Grounds 1-4, alleging obviousness, fail because they rely on post-hoc knowledge of the '504 patent's unique claimed sequence to reconstruct that invention piecemeal from 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.”)).

For example, Samsung's Grounds 1 and 2 contend that a POSA would have been motivated to combine Bowdish and Evans by starting with Bell, which teaches that eculizumab is a “particularly useful” antibody treatment of PNH.” (ALXN2104, 90:19-91:2.) But Bell does not direct a POSA to Bowdish. Instead, Bell—like the other pertinent prior art as of March 15, 2007—informed a POSA that “eculizumab” was Thomas's IgG4 antibody. Neither Samsung nor Dr. Ravetch provide a legitimate explanation as to why a POSA would have ignored Bell's clear and unequivocal direction towards Thomas's IgG4 antibody and

instead looked to Bowdish, which does not mention “eculizumab,” does not cite Bell (nor does Bell cite Bowdish), and does not mention if any of its disclosed antibodies bind C5. Even if a POSA looked to Bowdish after Bell (which is unlikely), nothing in Bowdish or Evans indicated to a POSA that either reference, alone or in combination, disclosed the specific, full-length, uniquely-engineered “eculizumab” antibody. A POSA would have had no reason to jump from Bell to the combination of Bowdish and Evans to learn anything about the structure or sequence of “eculizumab.”

Samsung’s Grounds 3 and 4 use improper hindsight to recreate the claimed sequence of the ’504 patent from sequences plucked from Evans and Mueller PCT (EX1009). Mueller PCT 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 implicitly noted, Mueller identified only an IgG4 isotype antibody (*i.e.*, the isotype of Thomas) as an “anti-C5 antibody,” and taught nothing about the C5 binding or clinical properties of “h5G1.1 CO12 HuG2/G4 mAb.” (Paper No. 9, 19.) There’s also no reference to C5 when Mueller discusses hybrid IgG2/IgG4 antibodies. Mueller also had its own reason for engineering a hybrid IgG2/G4 constant region,

which was specific to Mueller's xenograft rejection studies and had nothing to do with binding C5 or treatment of PNH.

A POSA would also not have been motivated to combine sequences from Evans and Mueller in such a way to arrive at the claimed sequence, because, as this same Panel previously explained in the Amgen IPRs, there is "no express link between the teachings of Mueller and Evans." (IPR2019-00739, Paper 15, 52.) Moreover, this Panel in the Amgen IPRs was left asking why a skilled artisan would choose the "somewhat tenuous" combination of Mueller and Evans, then "choos[e] precisely those portions of Evans's and Mueller's constructs to create an antibody having exactly the sequences set forth SEQ ID NOs: 2 and 4." (IPR2019-00739, Paper 15, 54.) "Patent Owner's argument regarding improper hindsight ma[de] some sense" to this Panel before. (IPR2019-00739, Paper 15, 54.) Here, however, it takes the opposite view without explaining its inconsistencies.

Samsung's Ground 2 and 4 also fail 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. Samsung also fails to appreciate the breadth of

potential formulations suggested by the combination of Bell and Wang, and focuses on unsupported considerations such as convenience and waste, rather than a formulator's primary consideration, stability.

Samsung's Ground 5, styled as inherent anticipation, fails because Bell does not inherently, or expressly, disclose all the elements recited in claims 1-5 and 7-10 of the '504 patent. As this Panel correctly recognizes, Bell uses the word "eculizumab" throughout its disclosure without ever expressly explaining more than that it is an "anti-C5 antibody . . . h5G1.1-mAb." (Paper No. 9, 49.) The Board also implicitly acknowledges that although Bell discusses eculizumab as a "particularly useful . . . therapy for PNH patients," it never expressly describes what eculizumab is. (Paper No. 9, 49.) Indeed, this Panel has already implicitly acknowledged that Bell cannot be anticipatory of the claimed sequences by stating "Bell uses the word 'eculizumab' at least 25 times throughout its disclosure, describing it as an anti-C5, h5G1.1-mAb, but without further expressly describing its structure." (Paper No. 9, 48.)

Yet, this Panel reasons that Bell did not need to disclose what eculizumab is because its reference alone would invoke "an understanding of the antibody in the ordinarily skilled artisan"—an unmistakable obviousness argument to support a Ground based on inherent anticipation. (Paper No. 9, 55.) Moreover, this Panel

also finds there to be “no dispute here that eculizumab, as disclosed by Bell, is the claimed antibody.” (Paper No. 9, 54.) But that statement by the Panel ignores two critical and undisputed facts: (1) Bell does not disclose a single amino acid sequence; and (2) when Bell mentions “eculizumab” it refers to Thomas’s IgG4 antibody.

Additionally, there is nothing in Bell showing that the sequences recited in the claims were publicly disclosed during the clinical trial, and in fact, the evidence says the opposite. (EX1002, 1347, 1324-27 at ¶¶ 6-13.)

In his deposition, Dr. Ravetch’s initial position was that “Thomas does not use the term ‘eculizumab,’ nor does he use the term ‘h5G1.1-mAb’ in his publication” and thus assumed that the “nomenclature [“h5G1.1-mAb”] is now being defined in Bell as being eculizumab, and it points us to the Evans reference.” (ALXN2104, 91:20-25.) But, once shown that Thomas (EX1010) **does** use the term “h5G1.1-mAb,” Dr. Ravetch attempted to wave it away as Thomas’s description of “the Fab” fragment, not a reference to Thomas’s full, intact IgG4 antibody. (ALXN2104, 97:6-18.) Dr. Ravetch’s explanation is inaccurate and inconsistent. As he later explained, Thomas (EX1010) uses the terminology “5G1.1 HuG4 . . . to refer to the intact antibody.” (ALXN2104, 97:19-23.) Thomas also states that “the avidity of this humanized antibody (h5G1.1 HuG4)”

was “compared to the murine 5G1.1mAb” and, in the next sentence, that “[t]he humanized h5G1.1 mAb had a two-fold lower avidity than the murine antibody.” (EX1010, 1396.) Thus, in his paper Thomas equated “h5G1.1 HuG4” with “h5G1.1 mAb.”

Dr. Ravetch also confused other instances of the different uses of “5G1.1” throughout the art. For example, within the context of Tacken (EX1044), he explained that the “nomenclature is interchangeable” between “h5G1.1-mAb” and “5G1.1” (ALXN2104, 186:4-13) and, to add further ambiguity, stated that such nomenclature “has been used in other publications with different specificity.” (ALXN2104, 187:5-8.) Though it is true that the precise meaning of the various “5G1.1” terms depends on the context in which it appears, Dr. Ravetch’s interpretation of those terms during his deposition seemed to morph into whatever was convenient for his opinions.

II. BACKGROUND

A. SOLIRIS[®] and Its Use to Treat PNH

The FDA approved SOLIRIS[®] on March 16, 2007, as the first approved therapy to reduce hemolysis in patients with PNH. (See ALXN2100, 1256; ALXN2005, 1.)

SOLIRIS[®] works by binding with high “affinity” (*i.e.*, tightness) and “specificity” (*i.e.*, directed to a single antigen) to C5. Without SOLIRIS[®]

treatment, the body naturally cleaves C5 into components “C5a” and “C5b,” which lead to downstream effects of the complement pathway, including hemolysis in PNH patients. When SOLIRIS[®] is administered, however, it binds to a critical location (“epitope”) on C5 with sufficient affinity and specificity to prevent cleavage of C5, thus blocking the effects of the complement pathway and sparing PNH patients’ red blood cells from destruction. (See ALXN2100, 1257.)

B. Monoclonal Antibodies for Human Therapy

As of March 15, 2007, antibodies were known to be complex three-dimensional proteins consisting of four polypeptide chains—two identical “heavy chains” and two identical “light chains”—forming a flexible Y-shaped structure. (ALXN2007, 110; ALXN2098, 5-7.) Additional background information on an antibody’s three-dimensional structure can be found in Alexion’s Patent Owner Preliminary Response, Paper No. 6, at 5-7.

IgG is the most abundant class of naturally-occurring antibodies in humans, and as of March 15, 2007, was the most common class used for human therapy. (ALXN2007, 105; ALXN2098, 4; EX1044, 2-5.) As depicted in Figure 1 (adopted from Samsung’s Petition), IgG constant regions can be subdivided into different parts, including a light chain constant region C_L, and heavy chain constant regions C_H1, the “hinge” region, C_H2, and C_H3.

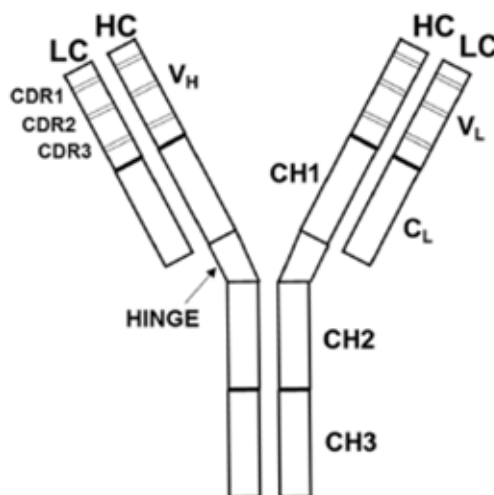


Figure 1: Basic structure of an IgG antibody

(See ALXN2022, ¶¶ 63-69.)

IgG antibodies are further distinguished by subtype within their class or isotype. Human IgG has four subtypes: IgG1, IgG2, IgG3, and IgG4.

(ALXN2007, 105; EX1044, 5.) The various subtypes differ structurally in the amino acid sequences of their heavy chain constant regions, the number and location of their disulfide bonds, and the lengths of their “hinge” regions. (See, *e.g.*, ALXN2008, 172; *see also* ALXN2009, 13924; *see also* EX1044, 5.) As of March 15, 2007, humanized monoclonal antibodies approved by the FDA were predominantly of the naturally occurring IgG1 or IgG4 subtypes, and all used one of the naturally occurring IgG constant regions. (See, *e.g.*, EX1044, 2-4, Table 1; ALXN2022, ¶ 81.)

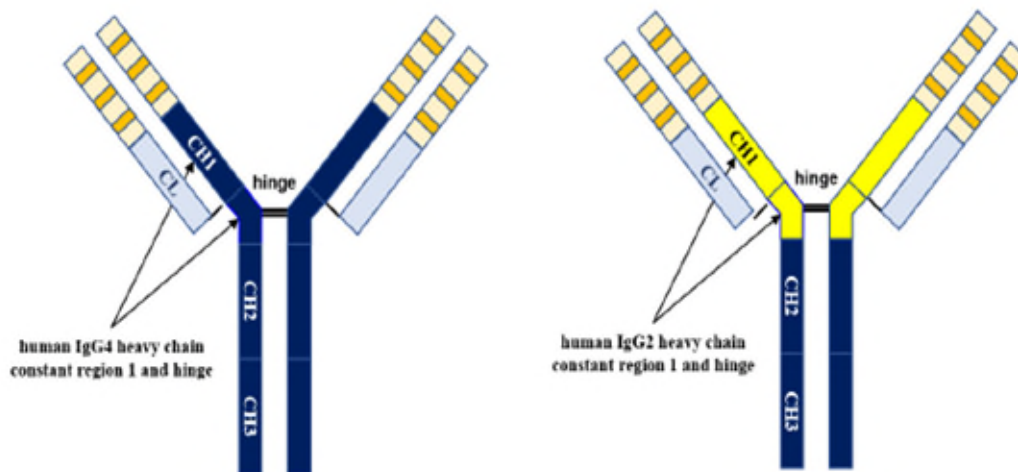
As Dr. Casadevall explains, “a POSA as of March 15, 2007, would have known that full-length, intact IgG antibodies have a prolonged plasma half-life relative to scFv and Fab fragments, due to their larger size and receptor interactions with the “Fc” region that is absent in the fragments.” (ALXN2022, ¶ 94.) As also explained by Dr. Casadevall, “[i]n addition to potentially affecting binding, by March 15, 2007, a POSA would have understood that switching to a uniquely-engineered, non-naturally occurring heavy chain constant region, such as a hybrid IgG2/G4 sequence, could also raise heightened immunogenicity concerns since it could have been perceived by the immune system as antigenically ‘foreign.’” (ALXN2022, ¶ 116.)

C. Structure and Design of the Clinically Tested “Eculizumab” Antibody, as Understood by a POSA as of March 15, 2007

A POSA as of March 15, 2007 would have understood that Alexion had developed a humanized antibody named “eculizumab,” which bound to human C5 and blocked its cleavage, and was shown in Phase II and Phase III human clinical trials to be safe and effective for the treatment of PNH. (EX1011, 552, 558; EX1013, 2559, 2564; EX1014, 1239, 1241-1242.) But a POSA at that time would *not* have known that “eculizumab” had the hybrid ***IgG2/G4*** sequence disclosed in SEQ ID NO: 2 and claimed in the ’504 patent.

Instead, the literature as of March 15, 2007 repeatedly taught a POSA that “eculizumab” contained the “***IgG4***” C_H region described in Thomas (EX1010). (See, e.g., EX1011, 553 (citing EX1010 (Ref. No. 15)); EX1013, 2559 (citing EX1010 (Ref. No. 9)); EX1014, 1234 (citing EX1010 (Ref. No. 13)); EX1007 ¶ [0052] (citing EX1010); EX1023 at, 1018 (citing EX1010 (Ref. No. [258884])).) The differences between eculizumab’s IgG2/G4 sequence (right) and Thomas’s IgG4 sequence (left) are shown in Figure 2:

Figure 2:



(See ALXN2022, ¶¶ 135-137.)

As described by the Thomas paper, the “***IgG4***” C_H region was selected for the anti-C5 antibody because the IgG4 subtype was thought to avoid activating human complement. (EX1010, 1396, 1399.)

Thomas reported data showing that the IgG4 humanized antibody had suitable affinity and specificity, and was as effective as the original mouse antibody (termed “murine 5G1.1” or “m5G1.1”) in an *in vitro* assay showing activity of blocking C5 cleavage and preventing lysis of blood cells due to complement activity. (EX1010, 1396; *see also* ALXN2022, ¶¶ 123-124.) Dr. Ravetch agreed that Thomas discusses a humanized antibody “on the route to a potential therapeutic” because it shows “that the 5G1.1 CDRs in a human framework context are able to retain their binding affinity and ability to prevent the activation of C5 cleavage.” (ALXN2104, 81:3-18.)

D. Structure and Sequence of SOLIRIS® Was Not Known Before March 15, 2007

Today, but **not** before the March 15, 2007 priority date for the ’504 patent, it is known that SOLIRIS® has the amino acid sequence recited in the ’504 patent’s claim 1, namely, “a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.” A POSA before the ’504 patent, however, would not have reasonably expected that an antibody consisting of SEQ ID NOs: 2 and 4 would work to not only bind C5, but to bind it with sufficient affinity and specificity to prevent its cleavage, or that it would safely and effectively treat conditions such as PNH.

As understood today, but not as of March 15, 2007, 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—designed by scientists at Alexion and thoroughly tested in clinical trials. (ALXN2100, 1257-1258.) Notably, SOLIRIS[®] was the first FDA-approved product containing Alexion’s uniquely-engineered C_H region. A POSA as of March 15, 2007 would not have been aware of any published clinical testing showing that an antibody with this uniquely-engineered constant region retained an ability to “bind[] C5” as required by claim 1 and would still be safe and effective for human therapeutic use.

Samsung’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.” To support its assumption that a POSA would have known that “eculizumab” contained an IgG2/IgG4 constant region, Samsung relies on a *single*, ambiguous sentence in just one document—Tacken (EX1008)—regarding an “isotype control antibody.” But a POSA looking for the structure of “eculizumab” would not have considered or credited Tacken above the overwhelming evidence in earlier and later publications that expressly identified

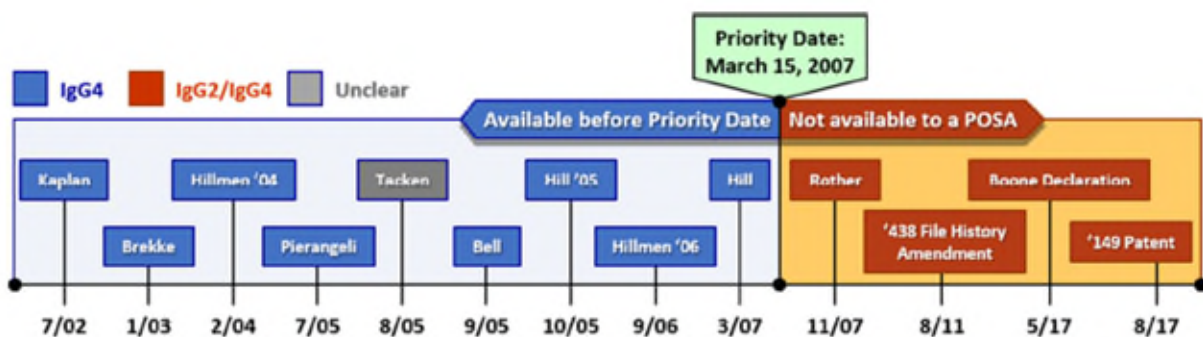
“eculizumab” as Thomas’s IgG4 antibody. (See Section III.A.1.) Indeed, Tacken itself cites to Thomas.

Tacken is the **only** document before March 15, 2007 that purportedly associated “eculizumab” with a hybrid IgG2/IgG4 constant region. But unlike the clinical literature discussed in Section III.A.2, Tacken did not concern the study of “eculizumab” in binding C5, blocking C5 cleavage, or treating conditions such as PNH. (ALXN2022 ¶¶ 141-151.) 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 to improve vaccinations. (EX1008, 1278-79, 1283-84.) Although Dr. Ravetch speculated that a POSA would run a “search of eculizumab and find Tacken” (ALXN2104, 120:15-19), the single reference to “eculizamab [sic]” in Tacken is misspelled, thus relegating Dr. Ravetch’s opinion to speculation. (EX1008, 1279.)

Samsung also never explains how—even if a POSA were somehow to ignore the literature and try to make an IgG2/IgG4 antibody that “binds C5” as claimed—which specific amino acids would be taken from IgG2 as opposed to IgG4, and why. A POSA would only be able to reconstruct the exact sequence of SEQ ID NOs: 2 and 4 using impermissible hindsight using the challenged patent as a guide.

This Panel’s statement that Tacken’s research was supported by “funding from Alexion Pharmaceuticals” has no bearing on, and is irrelevant to, the ultimate determination that the Board must make. (Paper No. 9, 38.) Moreover, the Board’s overreliance on Tacken is inapposite with Samsung’s limited use of the reference for background, and ignores the overwhelming weight of evidence, both before and after Tacken’s publication, and also within Tacken itself, directing a POSA to an entirely different antibody. (EX1008, 1279 (referring to Thomas as reference 19); *see also* Table 1; ALXN2022 ¶¶ 141-151.)

According to the following timeline, the **only** plausible conclusion a POSA could have reached in view of the entire content of the art was that “eculizumab” was Thomas’s IgG4 antibody (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, its Prosecution History, and the Prosecution of Related Applications

An overview of the '504 patent was provided in Alexion's Patent Owner Preliminary Response, Paper No. 6.

As relevant here, in the course of the '504 patent's prosecution, as well as prosecution of the related '880 patent, '149 patent, '189 patent, and, '809 patent, the Examiner considered the same, or substantially the same, prior art and arguments that Samsung now asserts in its Petition. In doing so, the Examiner made findings undermining Samsung's positions in its Petition, including that (1) none of the art recited an antibody with a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4, and (2) a POSA "would not have been easily guided to mak[e] antibodies with these recited sequences." (EX1002, 1347.) The Examiner also found that SOLIRIS[®] and its unique sequence was not "accessible to the public" as of March 15, 2007. (*Id.*)

For example, in finding the claims of the '504 patent to be novel and nonobvious, the Examiner:

- Expressly discussed Samsung's asserted references Evans (EX1005) and Wang (EX1044), as well as Hillmen 2004 (EX1011) (which is cumulative in all material respects here to Samsung's asserted

reference Bell (EX1007)), before finding the claims allowable (*see, e.g.,* EX1002, 1036-1040, 1118-1123, 1295-1300);

- Considered Samsung’s asserted reference Bell (EX1007), which Alexion submitted to the PTO (*see, e.g.,* EX1002, 827);
- Considered U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Samsung’s cited “Bowdish” application (EX1004), disclosing the same information on which Samsung relies here (*see, e.g.,* EX1002, 826); and
- Considered the Mueller 1997 article (EX1006), which is cumulative of Samsung’s asserted Mueller PCT reference (EX1009) because it discloses the same antibodies as Mueller (*see, e.g.,* EX1002, 106⁴; ALXN2022, ¶ 167).

Notably, during prosecution of the ’504 patent and related patents, the Examiner confirmed a central fact that both Samsung and this Panel now ignores—that Hillmen 2004 (like Bell), in describing “eculizumab” as a humanized anti-C5

⁴ Dr. Ravetch acknowledges that Mueller PCT is a “**companion**” patent application describing the **same work** published in the Mueller 1997 article.” (EX1003, ¶¶ 62, 94.)

antibody, cites to **Thomas** (i.e., “reference number 15” of Hillmen 2004) as “disclosing more information about eculizumab.” (ALXN2103, 1038, 1118 (citing EX1011); *see also* EX1002, 1036 (Examiner stating that “Hillmen . . . teaches that ‘eculizumab’ is a recombinant humanized antibody that binds to C5 . . . and cites **Thomas**”).) Alexion also submitted a declaration of co-inventor Dr. Leonard Bell during prosecution of the ’504 patent, explaining how a POSA reading Hillmen’s reference to Thomas would have been guided toward an antibody with a “naturally-occurring IgG4 heavy chain,” and would not have envisioned the very different antibody of the ’504 patent. (ALXN2103, 1079-1080, 1084 ¶¶ 3-5.) Ultimately, the Examiner agreed that the prior art did not disclose or suggest the specific antibody sequence claimed in the ’504 patent. (EX1002, 1347; *see also* ALXN2103, 1347.)

Samsung and this Panel also ignore the Declaration of Dr. Laural Boone (EX1002, 1320-27 (“the Boone Declaration”)), which the Examiner credited as showing that Alexion’s clinical studies of the claimed antibody did not disclose its sequence or render it publicly accessible. (EX1002, 1347-48.) In particular, the Examiner relied on Dr. Boone’s showing that the clinical studies of SOLIRIS® had rigorous confidentiality provisions, that “neither doctors nor patients had any knowledge of the . . . claimed sequences of the antibody used in the studies,” and

that “strict control . . . was exercised” over the study drug, which was “stored in a secure, limited-access storage area.” (EX1002, 1347, 1324-27 ¶¶ 6-13.) While, as Dr. Boone explained, it is known **today** that SOLIRIS[®] as used in these studies had the claimed sequence (EX1002, 1324 ¶ 6), a POSA as of March 15, 2007 would have only been guided by what was reported in the published literature, *i.e.*, that none of Bell, Hillmen (EX1011), or Hill (EX1013), which disclosed the results of clinical trials involving “eculizumab,” disclosed an amino acid sequence of “eculizumab” and all instead pointed to Thomas’s IgG4 structure as being “eculizumab.”

In view of all the art, Alexion’s submission of multiple declarations, and Alexion’s thorough response to the Examiner’s “Rule 105” request for information, the Examiner found that neither the SOLIRIS[®] drug product nor its complete sequence was in the public domain before March 15, 2007, and accordingly allowed the ’504 patent. (EX1002, 1347-48.)

III. **SAMSUNG MISSTATES THE SCOPE AND CONTENT OF THE ART IN HINDSIGHT**

For obviousness, the scope of the pertinent prior art is determined from the perspective of a POSA without hindsight, and includes the full scope of art pertaining to “the problem facing those skilled in the art at the time the invention was made.” *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015).

In defiance of these standards, Samsung describes the state of the art before March 15, 2007 in a way that is unduly selective and strategically crafted based on Samsung's hindsight knowledge of the claimed sequence. Samsung errs by "[d]efining the problem in terms of its solution" and using "improper hindsight in the selection of the prior art relevant to obviousness." *See, e.g., Insite Vision*, 783 F.3d at 859 (citing *Monarch Knitting Mach. Corp. v. Sulzer Morat, GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998)). Using its hindsight knowledge, Samsung at once (1) unduly narrows the scope of the art, by disregarding its teachings concerning the anti-C5 "eculizumab" antibody shown to safely and effectively treat PNH, and (2) unduly broadens the "state of the art," by selecting documents having nothing to do with the design of antibodies for blocking C5 cleavage or treating PNH.

A. Samsung Uses Hindsight to Disregard the Prior Art's Consistent Description of the "Eculizumab" Antibody Shown to Treat PNH as Thomas's IgG4 Antibody

Samsung reveals its hindsight analysis by failing to address the prior art's teachings as of March 15, 2007 regarding the structure and amino acid sequence of "eculizumab." A review of the prior art regarding "eculizumab" (including Samsung's own cited references) from the perspective of a POSA as of March 15, 2007, without hindsight bias, leads to only one consistent conclusion: that a POSA would have thought "eculizumab" to be Thomas's humanized IgG4 antibody. (See

Table 1.) Each of Samsung, Dr. Ravetch, and this Panel dismisses that straightforward conclusion. Instead, each favors what this Panel has dubbed the “reverse engineering” of the “eculizumab” sequence from a patchwork of non-analogous or irrelevant art based on the post-priority date knowledge that the patent discloses a hybrid sequence.

Accordingly, Samsung and the Board err by ignoring what the art actually taught a POSA about “eculizumab,” and instead use hindsight to read the term “eculizumab” into other documents that never even mention that word.

**1. Samsung Ignores the Art’s Teaching that
“Eculizumab” Was Described by Thomas**

The most glaring evidence of Samsung’s hindsight bias is its failure to acknowledge that *its own cited art*—including the Bell reference and other descriptions of Phase II and Phase III clinical studies showing the safety and efficacy of “eculizumab” for treating PNH—consistently cited to Thomas for details regarding the structure and design of “eculizumab.” It is undisputed that Thomas taught an ***IgG4*** antibody that is different from the uniquely-engineered ***IgG2/G4*** antibody reflected in the ’504 patent’s claimed sequence.

The following table exemplifies Samsung’s cited literature that described “eculizumab” as Thomas’s IgG4 antibody:

Table 1: “Eculizumab” References to Thomas in Samsung’s Pre-March 15, 2007 Cited Literature

Samsung’s Exhibit	Relies on Thomas’s IgG4 as “Eculizumab”	Statement Identifying “Eculizumab” as Thomas’s IgG4
Hillmen 2004 (EX1011), 553	✓	In reporting on a Phase II clinical trial for PNH, cites Thomas , Ref. No. 15, as describing “[e]culizumab” as “a recombinant humanized monoclonal antibody” that “binds specifically to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b. . . .”

Samsung's Exhibit	Relies on Thomas's IgG4 as "Eculizumab"	Statement Identifying "Eculizumab" as Thomas's IgG4
Hill 2005 (EX1013), 2559	✓	In reporting on a Phase II clinical trial for PNH, cites Thomas , Ref. No. 9, as describing "[e]culizumab" as "a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage."
Hillmen 2006 (EX1014), 1234	✓	In reporting on a Phase III clinical trial for PNH, cites Thomas , Ref. No. 13, as describing "[e]culizumab" as "a humanized monoclonal antibody directed against the terminal complement protein C5."

Samsung's Exhibit	Relies on Thomas's IgG4 as "Eculizumab"	Statement Identifying "Eculizumab" as Thomas's IgG4
Bell (EX1007), [0052]	✓	In a patent application describing results of Phase II clinical trials for PNH, cites <i>Thomas</i> as describing "[m]ethods for the preparation of h5G1.1-mAb," also identified "under the tradename eculizumab."
Kaplan (EX1023), 1018	✓	Cites <i>Thomas</i> , Ref. No. [258884], for synthesis of "[h]umanized 5G1.1," also identified as "eculizumab."
Tacken (EX1008), 1279	✓	Cites <i>Thomas</i> , Ref. No. 19, as describing the antibody "h5G1.1-mAb (5G1.1, eculizumab; Alexion Pharmaceuticals)"

(See ALXN2022, ¶¶ 123-24.)

Notably, all of Samsung's Grounds include the Bell reference teaching that the clinically safe and effective "eculizumab" antibody was Thomas's IgG4 antibody. Even Samsung cites Thomas multiple times in its discussion of the development of the eculizumab as an "h5G1.1 HuG4" antibody. (Petition, 9-10.) And Grounds 1-4 also include Tacke's reference to Thomas. That alone should support the validity of the claims of the '504 patent.

2. Nothing Samsung Cites Contradicts the Art's Teaching that the Clinically Effective and Safe "Eculizumab" Antibody Was Thomas's IgG4 Isotype

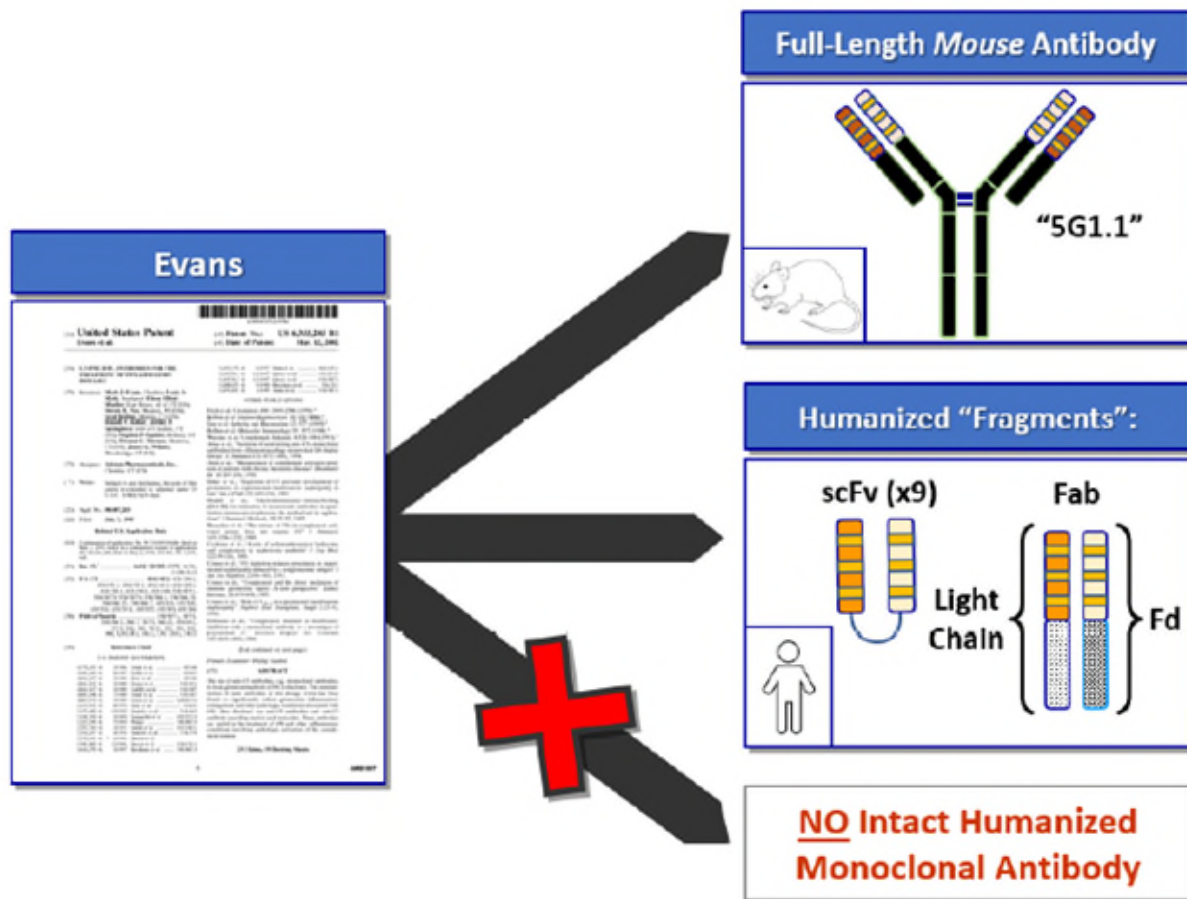
Samsung's arguments attempt to reconstruct the '504 patent's invention using hindsight knowledge of the claimed amino acid sequence—picking and choosing from documents that a POSA would never have reviewed for information regarding the complete structure of "eculizumab." *See, e.g., Merck Sharpe & Dohme 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."); *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.* 725 F.3d 1341, 1352 (Fed. Cir. 2013) ("Obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.").

**a. Evans Doesn't Teach the Claimed Sequence
of "Eculizumab" or Contradict Thomas**

Samsung suggests that "eculizumab" was somehow disclosed or claimed by the Evans patent (*e.g.*, Petition, 20-21, 31-34), but it is undisputed that Evans neither used the term "eculizumab," nor disclosed the heavy chain or full sequence of the antibody claimed by the '504 patent. (ALXN2104, 116:21-117:14, 118:24-119:5.) As Samsung concedes, Evans' Example 11 provides nine different versions of a humanized "variable" region for anti-C5 antibodies, with no guidance as to which, if any, were being used in antibodies developed for clinical trials. (*See, e.g.*, EX1005, 43:6-45:4; Petition, 21, 30.) In fact, Evans did not provide testing data for any one of the nine. Further, Evans only describes antibody constant regions generically (*e.g.*, stating that IgG constant regions are preferred), without identifying any specific heavy chain constant region that could or should be used. (EX1005, 45:24-33.) Nothing in Evans suggests or discloses constructing the uniquely-engineered heavy chain of the '504 patent's SEQ ID NO: 2.

To the extent Evans described "humanization" work based on the "5G1.1" mouse antibody, it was in the development of recombinant "fragments"—scFv or Fab—that did **not** contain an intact C_H region, let alone the uniquely-engineered heavy chain reflected in SEQ ID NO: 2 of the '504 patent. (EX1005, Example 11; ALXN2022 ¶ 128.) 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, (EX1005, 43:6-14, 43:62-45:4), and humanized “Fab” fragments that also lack the “Fc” portion (regions C_H2 and C_H3) of an intact antibody (EX1005, 43:21-61). (ALXN2022 ¶¶ 126.) Notably, Evans’ humanized Fab fragments have different heavy chain sequences (“Fd,” Evans SEQ ID NOs: 11 and 12) from the claimed sequence, including in the “C_H1” 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.



b. Neither Bowdish nor Mueller Discloses the Claimed Sequence of “Eculizumab” or Contradicts Thomas

According to Dr. Ravetch, a POSA would have been motivated to seek out the sequence of an antibody called “eculizumab” based on the promising clinical trial results reported in Bell, Hillmen (EX1011) and Hill (EX1013). (ALXN2104, 107:23-108:4, 119:6-18.) Following Dr. Ravetch’s own path, a POSA would not have been led to either Mueller PCT (or Mueller 1997) or Bowdish. Samsung cannot explain why a POSA would have turned to Bowdish or Mueller for a

description of “eculizumab” at least because, critically, neither Bowdish nor Mueller mention the term “eculizumab.” (ALXN2104, 145:7-8, 164:25-165:2.) Nor do either Bowdish or Mueller teach an antibody that binds C5 as recited in the claims of the ’504 patent, or that the antibodies that each reference does disclose would work to prevent C5 cleavage or safely and effectively treat PNH. There is no reason why a POSA would have set aside the literature’s clear teaching regarding the structure of the therapeutically successful “eculizumab” antibody disclosed in Thomas and would have instead looked to the Bowdish and Mueller references addressing unrelated problems.

Mueller PCT, and the associated Mueller 1997, concerned an issue unrelated to the ’504 patent—developing antibodies to porcine VCAM molecules to block transplant rejection. (EX1009, 8:23-26, 37:22-36; EX1006, 441-444.) A POSA would not have looked to either Mueller references for guidance on designing antibodies for blocking C5 cleavage or treating PNH. Rather, Mueller described anti-pVCAM antibodies with “IgG4” and hybrid “IgG2/IgG4” isotypes, as well as negative “isotype control” constructs with the same IgG4 and IgG2/IgG4 constant region, but a substituted variable region that would not bind pVCAM. (EX1009, 12:19-32; EX1006, 442-443.) Samsung does not explain why a POSA reading

Mueller would have singled out the “HuG2/G4” and assumed it to be the isotype that was used in the clinically effective and safe “eculizumab” antibody.

More importantly, Mueller 1997’s studies started with investigating anti-pVCAM HuG4 antibodies to reduce xenograft rejection by inhibiting infiltrating leukocytes, including T cells, NK cells, and monocytes. (EX1006, 441, 444-46.) Mueller found that the anti-pVCAM HuG4 antibodies continued to “promot[e] increased adhesion of Fc receptor (FcR) positive cells such as U937 monocytic cells,” which was undesirable for the purpose of Mueller 1997’s studies. (EX1006, 441, 445-46 (“Both the HuG4 antibodies as well as the anti-human C5 HuG4 antibody bound to U-937 cells.”)⁵.) To inhibit this undesirable activity, Mueller 1997 constructed anti-pVCAM HuG2/G4 antibodies. (EX1006, 446-48.) Naturally, then, Mueller 1997 reconstructed the anti-human C5 HuG4 to have the

⁵ Notably, this sentence and the one immediately following it in Mueller 1997 are the only instances in that reference where Mueller suggests its **HuG4** negative control antibody has anti-human C5 activity. (EX1006, 446.) Nothing in either Mueller 1997 or Mueller PCT suggests that its negative control antibody retained anti-human C5 activity after Mueller overhauled that antibody’s structure to have the hybrid **IgG2/G4** constant region.

same HuG2/G4 structure as its anti-pVCAM HuG2/G4 antibody so that Mueller 1997 could continue to use it as a negative control. Nothing in Mueller 1997 suggests that the new anti-human C5 HuG2/G4 antibody retained any anti-human C5 activity after its reconstruction from a HuG4. Nor was that activity material in any way to Mueller 1997's studies. Moreover, Mueller 1997 did not investigate whether the new, unnatural, hybrid IgG2/G4 sequence would be immunogenic *in vivo*, or would be safe and effective at treating conditions like PNH.

Likewise, Bowdish concerned using an antibody—*any* antibody—as a “scaffold” to house a peptide (*e.g.*, the hormone thrombopoietin (“TPO”)), thereby providing greater stability and longer half-life for the peptide *in vivo*. (EX1004 ¶¶ [0005][0006].) The assays reported in Bowdish had nothing to do with C5 binding or blocking complement-mediated lysis. Rather, Bowdish assessed the binding of TPO-mimetic peptide (presented on an antibody scaffold) with a TPO receptor (the “cMpl receptor”), a biological interaction that is not part of the complement pathway. (EX1004 ¶ [0192].) As with the Mueller references, Samsung does not and cannot explain why a POSA seeking a safe and effective anti-C5 antibody would have looked to Bowdish. *See, e.g., Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013).

Samsung is mistaken in suggesting that use of the term “5G1.1” in Bowdish, or the term “h5G1.1” in Mueller, would have supplied any definitive information about the structure or sequence of “eculizumab.” (*See, e.g.*, Petition, 10-12.) As Samsung acknowledges, and as Dr. Ravetch confirmed at deposition, the term “5G1.1” was used broadly to refer to many different constructs such as, *e.g.*, the original mouse (“murine”) antibody identified by Alexion (*e.g.*, Petition, 9 (citing EX1010, 6-7)), and a wide variety of “humanized” constructs (also termed “h5G1.1”), including at least nine different variable region fragments (“scFv”) described in Evans (*e.g.*, Petition, 19-21 (citing EX1005, Example 11 (2) and (11)-(18))), as well as Thomas’s humanized IgG4 construct that the literature as of March 15, 2007 described as “eculizumab” (Petition, 9 (citing EX1010)). And even in its hindsight effort to connect the broad terms “5G1.1” or “h5G1.1” with “eculizumab,” Samsung relies on documents that identified “eculizumab” as Thomas’s IgG4 antibody. (*See, e.g.*, Petition, 6-8.) Thus, neither Bowdish’s reference to using “5G1.1” as a scaffold for a TPO-mimetic peptide (EX1004 ¶¶ [0066], [0191]), nor Bowdish’s citation to Evans (*id.* ¶ [0191]), would have explained to a POSA how Bowdish’s TPO-mimetic construct relates to the structure of “eculizumab,” including the structure of its heavy chain constant region (ALXN2022, ¶¶ 203, 208).

Nor would Bowdish or Mueller have taught a POSA as of March 15, 2007 anything about whether an antibody with the unique heavy chain of SEQ ID NO: 2 would have been safe for human use. Nothing in the art, including Mueller, would have motivated a POSA to abandon the antibody structure described in Thomas in exchange for a uniquely-engineered antibody with unknown efficacy and safety.

B. Samsung Ignores the Art Regarding the Complexity and Unpredictability of Designing Monoclonal Antibodies for Human Clinical Therapy

A POSA as of March 15, 2007 would not have had any motivation to alter the structure of “eculizumab” described in the art at that time, and would not have reasonably expected success in doing so. As discussed above, a POSA would have understood “eculizumab,” the antibody reported as preventing cleavage of C5 and safely and effectively treating patients with PNH, to be Thomas’s IgG4 antibody. (See Sections II.C, III.B.) Thomas predicted that its IgG4 antibody would be potent in preventing C5 cleavage and “minimally immunogenic in patients” (EX1010, 1399), and the published Phase II and Phase III clinical trials that referred to Thomas as describing “eculizumab” seemingly confirmed those predictions to a POSA. (See Sections II.C, III.B; ALXN2104, 81:3-18.)

With that knowledge, a POSA would have had no reason to deviate from the structure of “eculizumab” described in Thomas. A POSA would have understood

the complexity and unpredictability involved in designing monoclonal antibodies for human clinical therapy, where even certain small changes to the amino acid sequence (including in the “constant” regions) could significantly impact the antigen-binding affinity and specificity of an antibody, as well as the antibody’s clinical efficacy and safety. (See, e.g., ALXN2015, 506, 508; ALXN2017, 961-62.) Accordingly, a POSA would have known that assessing the suitability of such a modified antibody for human therapy would have required expensive and time-consuming human testing.

As of March 15, 2007, a POSA would have understood that there were substantial risks and unpredictability associated with changing the constant region isotype of a known antibody, even if the variable region were left unchanged. (See ALXN2022, ¶¶ 105-118). Specifically, the art described how such “isotype switching” could affect critical properties, such as antigen binding affinity and specificity. (See, e.g., ALXN2011, 2240, 2242 (showing that antibodies expressing the same variable regions but different C_H regions “bind [antigen] with ***significant differences in affinity***”); ALXN2008, 169, 171 Fig. 1 (noting that despite having identical variable regions, the constant region structures of four isotype subclasses tested “clearly influenced functional antibody affinity” and “[t]he exact mechanism for this phenomenon remains obscure”); ALXN2013,

1379, 1380-81, 1384-86 (presenting “unexpected” results indicating that “isotype switching may lead to loss of recognition of the original [antigen] as well as the recognition of new epitopes”); ALXN2010, 3 (summarizing studies from before March 15, 2007, and explaining how heavy chain isotype switching “is associated with altered specificity despite conservation of [the variable] region sequence”).) In particular, the art described how changes to the “C_H1” and “hinge” portions of the heavy chain could significantly impact antigen-affinity and specificity, even without changes to the variable region. (*See, e.g.*, ALXN2012, 3388, 3391-92; ALXN2009, 13917-18, 13924.)

A POSA would have also understood that switching to a uniquely-engineered, non-naturally occurring (*i.e.*, “foreign”) heavy chain, such as a IgG2/4 hybrid sequence, could present heightened immunogenicity concerns. In particular, a POSA would have known that administering an antibody with a “foreign” heavy chain isotype to human patients could potentially result in harmful immunogenic reactions. (*See, e.g.*, ALXN2015, 508.)

In view of these teachings in the art regarding the complexity and unpredictability of designing monoclonal antibodies for human therapies, Samsung cannot explain how a POSA as of March 15, 2007—understanding from the art that the “eculizumab” antibody shown to be safe and effective for treating PNH

was Thomas's IgG4 isotype—would have been motivated to create a novel antibody with potentially different clinical properties by instead using the uniquely-engineered heavy chain reflected in SEQ ID NO: 2. Nor can Samsung explain how a POSA would have reasonably expected to succeed in using an antibody that deviated from the “eculizumab” structure suggested by the prior art.

Crucially, as of March 15, 2007, there was not a single FDA-approved monoclonal antibody product featuring the uniquely-engineered heavy chain of SOLIRIS[®] (*see, e.g.*, EX1044, 2-4, Table 1), and there were no published clinical trials showing a POSA that antibodies with such a constant region were safe for human administration. SOLIRIS[®]—first approved **after** March 15, 2007—was the **first** FDA-approved antibody with its uniquely-engineered C_H region.

IV. A PERSON OF ORDINARY SKILL IN THE ART

Samsung contends that a POSA would have had “an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceuticals, or a related discipline, with at least two years of experience in the discovery, development, and design of therapeutic antibodies for use as potential treatments in human disease.” (Petition, 15-16.)

Alexion does not dispute Samsung's POSA definition—which the Board accepted (Paper No. 9, 23)—except to clarify 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.)

Under either description of a POSA, Samsung cannot prove unpatentability of claims 1-10 of the '504 patent under any of its five fatally flawed Grounds.

V. SAMSUNG FAILS TO SHOW UNPATENTABILITY OF ANY CHALLENGED CLAIM

A. Samsung's Ground 1 Fails Because It Cannot Show That Claims 1-5 and 7-10 Are Obvious Over Bell, Bowdish, and Evans in View of Tacken and Mueller PCT

Samsung's Ground 1 fails because Samsung cannot show how, without hindsight, a POSA would have been motivated to select and combine Bowdish and Evans, in view of Bell, Tacken, and Mueller PCT to obtain the claimed invention, or how they could have reasonably expected to succeed in doing so.

Samsung relies on impermissible hindsight bias, which the Supreme Court and the Federal Circuit have repeatedly warned against in evaluating obviousness. *See, e.g., Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966); *Monarch Knitting Mach.*, 139 F.3d at 881 (“Defining the problem in terms of its solution reveals improper hindsight in the selection of prior art relevant to obviousness.”); *Zoltek Corp. v. U.S.*, 815 F.3d 1302, 1313 (Fed. Cir. 2000) (warning against “the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher”). Here, Samsung and the Board use their

present-day knowledge of the '504 patent and the SOLIRIS[®] antibody claimed in the '504 patent to reconstruct its uniquely-engineered, non-naturally occurring amino acid sequence from bits and pieces of art, including the non-analogous “Bowdish” reference that a POSA without hindsight would have never considered. At the same time, Samsung ignores the art’s consistent teaching that “eculizumab” had an IgG4 constant region as described in Thomas. For this reason, Samsung’s Ground 2 must fail.

This Panel seems to accept wholesale Samsung’s explanation of the prior art’s description of what “eculizumab” is. (Paper No. 9, 37-40.) But Samsung’s explanation, and thus the Board’s reliance on it, is incorrect. This Panel’s extra emphasis on Bell’s cite to Evans simply because Evans appears before Thomas is legally irrelevant and misplaced. (IPR2023-00933, Paper No. 9, 45.) Bell refers to the preparation of both “h5G.1.1-mAb” and “***h5G1.1-scFv and other functional fragments.***” (EX1007, [0052].) Evans discloses the preparation of humanized ***5G1.1-scFv and other functional fragments.*** (EX1005, 42:55-49:48.) Further, Evans never refers to “***h5G1.1-mAb.***” Instead, Evans refers to “5G1.1 mAb,” which is the native mouse antibody. (EX1005, 50:3 (“the native ***murine*** 5G1.1 mAb”).) In contrast, Thomas discloses the preparation of “***h5G1.1-mAb.***” (EX1010, 013 (referring to the avidity of “h5G1.1 HuG4,” which Thomas also

refers to as “humanized ***h5G1.1 mAb***”).) Bell then refers only to “***h5G1.1-mAb***” (*i.e.*, Thomas’s antibody) as “undergoing clinical trials under the tradename eculizumab.” (EX1007, [0052].)

The same is true regarding Samsung’s and this Panel’s misplaced reliance on Tacken. Like Bell, Tacken refers to “h5G1.1-mAb” then cites to Thomas.

Tacken also cites to Mueller 1997, another publication by Alexion authors, as Samsung and this Panel have recognized. (Paper No. 9, 17, 38.) As discussed, Mueller 1997 studied anti-pVCAM antibodies and chose to construct anti-pVCAM HuG2/G4 antibodies for the specific purpose of inhibiting interaction with U-937 monocytic cells because those cells were not inhibited by Mueller’s IgG4 antibodies due to interaction with the HuG4 Fc region. (Section II.A.2.b.) Thus, Tacken’s negative control that “contain[s] the same IgG2/IgG4 constant region” is referring to Mueller 1997’s negative control. Indeed, like Mueller 1997, Tacken found “interactions between the targeting antibody and Fc receptors” undesirable. (EX1008, 011.) Notably, neither Samsung nor Dr. Ravetch have pointed to a single instance in the prior art that would provide a POSA with motivation to modify Thomas’s IgG4 construct to an IgG2/G4 because it is undesirable to bind Fc receptors when targeting human C5.

Moreover, the '504 patent's statement that Evans discloses "a preferred whole antibody, which was later named eculizumab" (Paper No. 9, 50) is irrelevant to an obviousness analysis, as it is using the '504 patent itself to provide information that the prior art does not. That is hindsight.

Samsung cannot explain why a POSA seeking to develop an anti-C5 antibody would ever have started with Bowdish—a reference having nothing to do with blocking C5 cleavage or treating PNH. *See Broadcom*, 732 F.3d at 1334 (affirming nonobviousness finding where the asserted art and the patent-in-suit "addressed two different problems"). Bowdish is not analogous art to the '504 patent. *See, e.g., Circuit Check Inc. v. QXQ Inc.*, 795 F. 3d 1331, 1335 (Fed. Cir. 2015) ("[D]isputed prior art can be analogous only if it is reasonably pertinent to the particular problem solved by the inventor."). Bowdish's TPO-mimetic constructs were not tested for, and were not intended to have, anti-C5 activity or efficacy in treating PNH; and the TPO activity of these constructs had nothing to do with the complement pathway or C5. Without hindsight, a POSA would have had no reason to "look to [Bowdish] to solve the particular problem at hand" that was solved by the invention of the '504 patent. *Circuit Check*, 795 F.3d at 1335.

Likewise, nothing would have guided a POSA to turn from Bell to Bowdish for the structure of "eculizumab." Samsung assumes that a POSA considering the

structure and sequence of Bell’s “eculizumab” would have (1) selected Bowdish, rather than Thomas, as a starting point despite the fact that Bowdish never mentions “eculizumab,” is not cited by Bell or any other prior art references defining “eculizumab,” and does not contain any C5-binding or clinical data suggesting that it might be associated with “eculizumab”; (2) identified Bowdish’s TPO-mimetic compound as relating to a humanized antibody with a hybrid IgG2/IgG4 constant region even though nothing in Bowdish contains such a statement; and (3) associated the purported IgG2/IgG4 structure of Bowdish’s TPO-mimetic compound with “eculizumab” despite the teaching in Bell itself, and the consistent teaching throughout the prior art, that a POSA would have understood “eculizumab” to be an IgG4 isotype antibody, which would not match with the sequence of a hybrid IgG2/IgG4 antibody.

Further, there is no basis for Samsung’s hindsight-driven contention that a POSA would have reverse-engineered “eculizumab” by substituting a heavy chain CDR3 sequence from Evans into the TPO-mimetic construct of Bowdish. *See, e.g., Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019) (“[W]orking backwards from [a] compound, with the benefit of hindsight, once one is aware of it does not render it obvious.”). Neither Bowdish nor Evans mentioned “eculizumab”—and Samsung’s assertions to the contrary further

confirm its reliance on impermissible hindsight. (See Section III.A.2.b.) Bowdish only refers to its TPO-mimetic scaffold as “5G1.1” (EX1004 ¶ [0191])—a broad term that a POSA understood to encompass a wide variety of possible murine and humanized antibodies and fragments, and that was in no way limited to “eculizumab.” (See Section III.A.2.b.) Evans, in turn, described only variable region fragments of anti-C5 antibodies, and did not describe the constant region of “eculizumab” or any other complete humanized anti-C5 antibody. (See Section III.A.2.a.) As Samsung admits, “Evans does not identify the specific sequence used in eculizumab by name” and suggests that a POSA should just try all of them. (Petition, 52.) But a POSA without hindsight would have had **no reason** to believe that combining Bowdish’s TPO-mimetic construct with one of the many sequences from Evans would lead to “eculizumab.” (See ALXN2022, ¶¶ 208-223.)

Samsung exacerbates its hindsight error by ignoring what the art (including Bell) **actually** taught a POSA as of March 15, 2007 about the structure and sequence of “eculizumab”: that it was consistently described by referencing Thomas, which disclosed an IgG4 isotype antibody. (See Table 1.) Samsung cannot explain why a POSA, without the benefit of hindsight, would have ignored the clear teachings of the art regarding the structure of “eculizumab,” and instead turned to non-analogous art such as Bowdish to experiment with different antibody

sequences that were **not** known to prevent C5 cleavage or safely and effectively treat PNH, and had not been studied in humans. Rather, the art's teaching that "eculizumab" had the IgG4 structure described in Thomas **taught away** from such unwarranted, unpredictable experimentation with the TPO-mimetic constructs of Bowdish (see ALXN2022, ¶¶ 223-230). *Millennium Pharms., Inc. v. Sandoz. Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017).

Even if Bowdish and Evans were combined as per Samsung's hindsight-driven theory, a POSA would not have reasonably expected the resulting compound to work at preventing C5 cleavage and safely and effectively treating PNH. See, e.g., *Novartis Pharm. Corp. v. West-Ward Pharms. Int'l Ltd.*, No. 2018-1434, 2019 WL 2079879, *7-8 (Fed. Cir. May 13, 2019). A POSA would have understood that even small changes to the amino acid sequence could have a substantial impact on the binding properties and the safety and efficacy of an antibody. (See Section III.A.) A POSA would not have reasonably predicted the activity, safety, or efficacy of the antibody that Samsung cobbles together in hindsight from Bowdish and Evans, which differs significantly from Thomas's IgG4 antibody described in the art as "eculizumab." Nor was there any reason for a POSA to undertake extensive testing of such an antibody, when the art taught that "eculizumab" (i.e., the IgG4 antibody described in Thomas) was already

thoroughly studied and shown to be a clinical success. (See ALXN2022, ¶ 233, Figure 14.) Notably, if consulted, both Bell and Tacke cited by Samsung in this Ground would also have led the POSA to the IgG4 antibody described in Thomas.

Mueller PCT, as an anti-pVCAM reference, would not even have been consulted. But even if it had been, Mueller also would have pointed the other way. As the Board previously noted in IPR2019-00739, Mueller identified **only** an **IgG4** isotype antibody (*i.e.*, the isotype of Thomas) as an “anti-C5 antibody,” and taught nothing about the C5 binding or clinical properties of “h5G1.1 CO12 HuG2/G4 mAb.” (Paper No. 15, 54.)

Samsung’s proposed sequence comparisons (Petition, 30-33) and “routine alignments” (Petition, 38-39) are again, the epitome of hindsight. A POSA would have had to work back from the claimed sequence to make any sense of these comparisons and alignments and would never have been motivated to make them in the first place given the disparate nature of the references: Bowdish (TPO-mimetic peptides), Mueller (anti-pVCAM antibodies), Evans (murine 5G1.1 antibody). *See TQ Delta, LLC v. Cisco Sys.*, 942 F.3d 1352, 1361-62 (Fed. Cir. 2019). Nor can Samsung explain why anyone would be motivated to run Bowdish’s TPO-mimetic peptide “through a protein sequence search” (Petition, 32) except with the benefit of hindsight and by ignoring the reference to Evans’

5G1.1 murine antibody.⁶ How a POSA would choose which portions of the sequence to search, how to search them, what database to use, and what the results would look like before March 15, 2007 also remain unexplained. Thus, adopting Samsung's Ground 1 arguments would be error.

B. Samsung's Ground 2 Fails Because It Cannot Show that Claim 6 Is Obvious Over Bell, Bowdish, Evans, and Wang in View of Tacke and Mueller PCT

With nothing in Bell, Bowdish, or Evans rendering obvious an antibody with the specific sequence recited in the claims 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. (ALXN2024,⁷

⁶ Samsung admits that Evans discloses "the original mouse antibody 5G1.1, which binds C5." (Petition, 40.)

⁷ The Trout Declaration (ALXN2022) was submitted in IPR2019-00739 in support of Alexion's Response. Although responsive to Amgen's Petition and expert declaration, the arguments contained in that Petition and declaration were substantially similar to those made here by Samsung, Dr. Ravetch, and Dr. Ippoliti. Therefore, Alexion cites to it for support here. In a new declaration, Dr. Trout has reaffirmed his opinions and authorized their use here. (ALXN2107.)

¶¶ 64-91; ALXN2022, ¶¶ 189-91.) 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, ¶¶ 189-91.) A POSA particularly would have had 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 or testing 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 (EX1044), which broadly concerned administration of a wide range of anti-C5 antibodies and fragments *by inhalation through a “nebulizer”* device for treating respiratory diseases.

(EX1044, ¶¶ [0169]-[0173]; ALXN2024, ¶¶ 81-83.) *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.) Wang also did not specifically teach “concentrations in the range of 1 to 30 mg/ml” as Samsung claims (Petition, 49) but rather suggested 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. (EX1044, ¶¶ [0067], [0130], [0170]-[0172], Fig. 10; ALXN2024, ¶¶ 84-86.)

Similarly, nothing in Bell disclosed a “300 mg single-usage dosage form.” (ALXN2105, 32:11-14.) Bell disclosed the administration of 600 mg and 900 mg dosages, but did not describe any particular dosage units or dosage forms. (ALXN2024, ¶¶ 91; ALXN2105, 32:4-10.)

To arrive at the specific composition of claim 6, Samsung argues that a 300 mg dose would have been obvious because 300 is a “common factor of 600 and 900,” and “[b]ased on simple arithmetic, 30 ml of a 10 mg/ml solution provides a 300 mg total dose.” (Petition, 44, 49.) Both Dr. Ippoliti and Dr. Ravetch agreed that Bell suggests many total dosages, because 600 and 900 are divisible by “many

other numbers” (ALXN2104, 100:16-18; ALXN2105, 45:21-46:5), and Wang teaches a “whole range” of concentrations (ALXN2104, 202:24-203:6; ALXN2105, 45:11-16). Dr. Ippoliti also agreed that a POSA could have reasonably followed a number of paths from Bell and Wang using such simple arithmetic. (ALXN2105, 65:4-11.) For example, Dr. Ippoliti acknowledged that formulations comprising a 100 mg total dose using 25 ml of a 4 mg/ml solution, and a 150 mg total dose using 30 ml of a 5 mg/ml solution are taught by the combination of Bell and Wang. (ALXN2105, 63:24-64:25.)

To overcome the broad dosage and concentration disclosures of Bell and Wang, Samsung and its experts simply assume that a POSA would be driven by additional considerations such as convenience, scaling, storage, and waste. (*See e.g.*, Petition, 44, 49; EX1062, ¶¶ 26, 51; EX1003, ¶¶ 148.) Dr. Ippoliti however, agreed that her opinions regarding such considerations lack support, and are not addressed by Bell or Wang. (ALXN2105, 32:15-33:3, 33:23-35:8, 35:22-36:2.) Moreover, Dr. Ippoliti explained that during formulation of an antibody, “[s]tability of the product is always the driver.” (ALXN2105, 56:17-23.) A POSA therefore, provided with a number of potential formulation paths based on Bell and Wang, would understand that the ’504 patent’s novel, uncharacterized antibody would have its own unique requirements for establishing stability, as

acknowledged by Dr. Ippoliti. (ALXN2105, 51:15-52:16.) Accordingly, without first testing the stability of the many formulations potentially encompassed by Bell and Wang, a POSA would have no reasonable expectation that the composition of claim 6 would be stable or work. Samsung's argument to the contrary requires impermissible hindsight using the '504 patent as a guide.

C. Samsung's Ground 3 Fails Because It Cannot Show that Claims 1-5 and 7-10 Are Obvious Over Evans and Mueller PCT in View of Bell and Tacken

Samsung attempts to combine Evans and Mueller PCT “in view of Bell and Tacken” to arrive at the claimed sequence. But again, the only actual antibody disclosed in Evans is the 5G1.1 murine antibody and Mueller PCT relates to an entirely different antibody directed at “pVCAM.” As the Board previously noted in IPR2019-00739, Mueller PCT identified *only* an **IgG4** isotype antibody (*i.e.*, the isotype of Thomas) as an anti-C5 antibody, and taught nothing about the C5 binding or clinical properties of “h5G1.1 CO12 HuG2/G4 mAb.” (Paper No. 15, 54.)

Nor would a POSA have been motivated to combine the sequences in Evans and Mueller PCT—neither of which cites to the other—in the exact manner to get the specific claimed antibody sequence of the '504 patent. As this Board correctly recognized in the Amgen IPRs, nothing in Evans or Mueller instructs 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 SEQ ID Nos: 2 and 4.” (IPR2019-00739, Paper No. 15, 54.) This Panel, the same Panel as in the Amgen IPRs, has now come to the opposite conclusion on the same record.

Just as in Ground 1, even if a POSA were somehow motivated to combine these disparate references, viewing them in light of the Bell and Tackén references of Ground 3 would have led the POSA even further astray as both of those references cited to Thomas’s HuG4 sequence for the sequence of the anti-C5 antibody eculizumab. As already noted, Bell’s reference to “h5G.1.1-mAb” is a reference to the antibody disclosed in Thomas. (EX1010, 013 (referring to the avidity of “h5G1.1 HuG4,” which Thomas also refers to as “humanized h5G1.1 mAb”).) Like Bell, Tackén refers to “h5G1.1-mAb” then cites to Thomas. Further, as already noted, Tackén’s negative control that supposedly “contain[s] the same IgG2/IgG4 constant region” is referring to Mueller 1997’s IgG2/IgG4 negative control, and there is nothing in either Mueller reference that suggests that its negative control antibody retained anti-human C5 activity after Mueller overhauled that antibody’s structure to have the hybrid IgG2/G4 constant region.

Mueller did not include any experiments or data on C5 binding, blocking C5 cleavage, or treating PNH. Insofar as Mueller described “h5G1.1” antibodies, with either IgG4 or “IgG2/G4” heavy chain constant regions, these were exclusively used as “isotype control” antibodies in studies measuring the activity of the anti-pVCAM antibodies. (EX1009, 9:6-9, 12:19-37; EX1006, 442-443, 448.) A POSA would have understood that Mueller could have used **any** antibody with an IgG4 or IgG2/G4 isotype as a “negative control” for its *in vitro* experiments, as long as it did not bind to pVCAM. Ultimately, this Panel, in the Amgen IPRs, concluded that “[i]t is not apparent that the skilled artisan, knowing of Evans, would have looked to Mueller, or vice versa.” (IPR2019-00739, Paper 15, 54.)

Nor can Samsung show that a POSA, without the benefit of hindsight, would have reasonably expected success with an antibody formed from combining a variable region from Evans with the “IgG2/G4” heavy chain constant region of Mueller PCT’s anti-pVCAM antibodies and “negative controls.” A POSA as of March 15, 2007 would have understood that “eculizumab”—the antibody shown to prevent C5 cleavage and safely and effectively treat PNH—was Thomas’s **IgG4** humanized antibody. (See Section III.A.1.) A POSA would have had no reason to deviate from what they understood to be the structure and sequence of “eculizumab,” and instead make an antibody with a different sequence that a

POSA would not have reasonably expected to still block C5 cleavage or be safe or effective for human administration to treat PNH. (See ALXN2022, ¶¶ 238-262.)

In fact, a POSA as of March 15, 2007 would not have known of **any** human clinical testing reporting the safety of antibodies using the “IgG2/G4” hybrid described in Mueller PCT, which only featured *in vitro* experiments.

Samsung again attempts to support its argument with hindsight sequence alignments and comparisons. (Petition, 53-55.) It picks and chooses a specific variable sequence from Evans’ Example 11, identified as “CO12,” combines it with the constant G2/G4 regions of Mueller PCT, and then compares it to the claimed sequences to argue obviousness. But nothing in Evans or Mueller PCT teaches that such a combination should be done, what it should be compared to, or whether it would result in a safe and effective anti-C5 antibody. Again, as this Panel previously recognized (IPR2019-00739, Paper 15, 54), Samsung’s combination is pure hindsight. (See, ALXN2022, ¶¶ 238-262.) A final written decision invalidating claims 1-5 and 7-10 of the ’504 patent based on such hindsight would be error.

**D. Samsung's Ground 4 Fails Because It Cannot Show that
Claim 6 Is Obvious Over Bell, Evans,
Mueller PCT, and Wang in View of Tacke**

Samsung's Ground 4 adds Wang to Ground 3's same unwieldy combination. Again, none of these references render obvious eculizumab's uniquely engineered sequence, and Wang and Bell fail to disclose the claimed formulation and administration limitations.

Ground 4 fails for the same reasons Ground 3 fails. A POSA would not have been motivated to start with Bell, which cites to Thomas, and combine Mueller PCT, which discloses an anti-pVCAM antibody, with Evans, which discloses only the 5G1.1 mouse antibody and multiple scFv's. The Board already rejected this argument. (See Section III.A.)

Samsung also cannot show how the other elements of claim 6 would have been obvious without hindsight. As with Ground 2, Samsung's arguments using Bell and Wang fail. (See Section III.B.)

**E. Samsung's Ground 5 Fails Because It Cannot Show that
Claims 1-5 and 7-10 Are Anticipated by Bell**

Samsung's Ground 5 fails because Bell does not expressly or inherently disclose all the elements recited in claims 1-5 and 7-10 of the '504 patent. See, e.g., *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002) (“[A]nticipation requires that each limitation of a claim must be found in a single

reference . . . [and] does not permit an additional reference to supply a missing claim limitation.”); *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.”).

Samsung openly admits that “Bell’s disclosure does not include the exact amino acid sequence of eculizumab . . .” (Petition, 29.) This Panel has also expressly admitted—twice—that Bell cannot anticipate because: (1) “Bell uses the word ‘eculizumab’ at least 25 times throughout its disclosure, describing it as an anti-C5, h5G1.1-mAb, **but without further expressly describing its structure**” (Paper No. 9, 48); and (2) although Bell discusses eculizumab as a “particularly useful . . . therapy for PNH patients,” it never expressly describes what eculizumab is. (Paper No. 9, 49.) Then, in order to “describe[] its structure,” Samsung and this Panel must cobble together multiple unrelated references. That is an analysis for an obviousness theory, not anticipation.

In circular fashion, Samsung merely restates its hindsight obviousness arguments in the guise of “enablement” to argue that Bell “inherently” disclosed the claimed sequence. (Petition, 61.) But neither this sleight of hand nor the supposed “admission” that “it is known today that SOLIRIS[®] as used in these studies had the claimed sequence of SEQ ID NOs: 2 and 4” (Petition, 59) can

change the fact that the sequence was **unknown** at the time of Bell’s publication and was disclosed there as corresponding to Thomas’s IgG4 isotype. As recognized by the Board in the Amgen IPRs, to the extent Bell disclosed anything about the structure of “eculizumab,” it would have directed a POSA towards an antibody with an **IgG4** heavy chain constant region—as did Hillmen, Hill, and the many other references pointing to Thomas for disclosure of “eculizumab.”

(IPR2019-00739, Paper No. 15, 29 n. 16.) Further, in the Amgen IPRs, this Panel found that Petitioner Amgen did “not carr[y] its burden to show a reasonable likelihood of anticipation of the claim of the ’504 patent” based on the Hillmen (EX1011) and Hill (EX1013) references, both of which are cumulative to Bell.

(IPR2019-00739, Paper No. 15, 28, 44.) There, this Panel reasoned that “eculizumab . . . refers to a class or category of anti-C5 antibodies,” not a single antibody structure as argued by Petitioner, and also that “Thomas’s disclosure of eculizumab in the IgG4 isotype [was] the first construction of eculizumab.”

(IPR2019-00739, Paper No. 15, 33.) Now, this Panel appears to contradict its past decision by minimizing the weight of the art’s pervasive citations to Thomas.

Significantly, Bell fails to disclose at least the element of “a heavy chain consisting of SEQ ID NO: 2.” While Bell described administering “eculizumab” for treating PNH, **nothing** in Bell taught the uniquely-engineered heavy chain

reflected in “SEQ ID NO: 2.” (See Section III.A.) Rather, Bell referenced Thomas’s ***IgG4*** antibody (*i.e.*, “h5G1.1-mAb”) that is a different sequence than that of SEQ ID NO: 2. In particular, Bell cited Thomas as describing “[m]ethods for the preparation of h5G1.1-mAb . . . under the tradename eculizumab”⁸ (EX1007 ¶ [0052]), and described positive Phase II clinical results for “eculizumab” in PNH patients (EX1007 ¶¶ [0081]-[0095]). Bell thus would have led a POSA away from other antibody constructs that lacked such published reports of clinical safety and efficacy, such as the uniquely-engineered, non-naturally occurring antibody claimed in the ’504 patent.

Moreover, this Panel’s statement that “Bell is ***explicit*** that ***Evans*** described ‘[m]ethods for the preparation of h5G1.1, h5G1.1-scFv and other functional fragments of h5G1.1” (Paper No. 9, 54) is inaccurate because Bell also cites to

⁸ While paragraph [0052] of Bell also cited Evans for the disclosure of antibody fragments, a POSA would have understood that Bell’s statements regarding the complete antibody “eculizumab” must refer to Thomas, not Evans, because Evans provided only antibody fragment sequences that did not include a heavy chain constant region, and Evans never mentions “h5G1.1-mAb.” (See, *e.g.*, EX1005, 43:6-14, 43:62-45:4; ALXN2104, 189:14-17.)

Thomas for that same proposition. As already discussed, Thomas discloses the preparation of “h5G1.1-mAb” and Evans discusses “h5G1.1-scFv and other functional fragments.” (See Section V.A.)

Accordingly, nothing in Bell discloses each and every element of claim 1 of the '504 patent. Nor could Bell have enabled a POSA to make and use the specific antibody recited in claim 1 without undue experimentation, because Bell (and all of the other art) guided a POSA to make and use a very different antibody—Thomas’s **IgG4** isotype antibody. See, e.g., *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) (for a reference to anticipate, “[i]t is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation”). (See ALXN2022, ¶¶ 195-199.)

Samsung, and the Board, implicitly concede that Bell did not disclose or enable the claimed invention, because Samsung’s theory of “enablement” requires a POSA to combine fragments of the claimed sequence from various other prior art documents, including, e.g., Evans, Bowdish, Mueller, and Tacken. (See Petition, 61-62; Paper No. 9, 48-55.) Samsung’s “enablement” arguments appear simply to be a restatement of the obviousness arguments that Samsung asserts under Grounds 1-4 that Samsung has improperly attempted to shoehorn into an alleged

anticipation argument. *See, e.g., Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002) (“[A]nticipation requires that each limitation of a claim must be found in a single reference . . . [and] does not permit an additional reference to supply a missing claim limitation.”). In any case, Samsung has failed to show that a POSA provided with Bell and the Evans, Bowdish, Mueller, or Tacke references as of March 15, 2007 would have been led to the ’504 patent’s claimed amino acid sequence without undue experimentation, when Bell, and the many other references listed in Table 1 taught a POSA that “eculizumab” was Thomas’s IgG4 antibody. (*See* Section III.A.1.)

Acknowledging that Bell failed to expressly disclose the claimed sequence of the ’504 patent, Samsung is forced to turn to non-prior art, post-filing information regarding the sequence of SOLIRIS[®], and attempts to read that information back into the prior art under the guise of alleged “inherent anticipation.” (*See, e.g.,* Petition, 58-61.) This Panel also falls victim to this type of hindsight by using “the ’504 patent, itself” as part of its analysis. (Paper No. 9, 50.) As explained below, however, Samsung’s inherent anticipation theory fails because it is premised on both a misapplication of the law and a misstatement of the pertinent facts.

In particular, Samsung alleges inherent anticipation on the grounds that **today**—years after the '504 patent's March 15, 2007 priority date—it is known that the clinical study underlying the Bell publication **actually** used an antibody with a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4. But Samsung is mistaken on the law. The mere naming of an investigational product (*e.g.*, “eculizumab”) in a prior art publication does **not** inherently anticipate later-filed patent claims detailing the specific structure or composition of that product (*i.e.*, SEQ ID NOs: 2 and 4), if a POSA could not have **necessarily** determined the later claimed structure/composition from the information publicly available as of the priority date. *See, e.g., Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-83 (Fed. Cir. 2018). Likewise, post-filing information showing that the later-claimed antibody sequence was actually used in the studies underlying prior art clinical publications is insufficient to give rise to inherent anticipation, especially when those prior art publications would have guided a POSA to a different sequence. *See, e.g., id.; Bayer CropScience LP v. Syngenta Ltd.*, IPR2017-01332, Paper 15, 3-6 (Apr. 2, 2018).

Accordingly, even if it is known today that the “eculizumab” antibody used in the clinical studies underlying the Bell publication was in fact the antibody recited in the '504 patent, Samsung has not shown inherent anticipation of the

claims. That is because Samsung fails to show that a POSA as of March 15, 2007 reading Bell would have ***necessarily*** known that the antibody used in those studies had the later-claimed amino acid sequence. *See Endo*, 894 F.3d at 1378-83. To the contrary, as discussed above, a POSA reading Bell would have envisioned that the antibody “eculizumab” was a very different antibody than what the ’504 patent claims, having Thomas’s “IgG4” heavy chain rather than the unique, non-naturally occurring heavy chain region reflected in “SEQ ID NO: 2.” (*See* Section III.A.1.) A publication’s use of the name “eculizumab” to refer to an antibody used in a clinical study does not constitute disclosure of the actual sequence of that antibody, particularly when a POSA as of March 15, 2007 would have understood that name to refer to a different sequence (*i.e.*, the sequence set forth in Thomas). *See, e.g., Bayer CropScience*, IPR2017-01332, Paper 15 at 3-6.

Nor could a POSA as of the priority date have independently determined the sequence of the antibody clinically tested in Bell. Rather, as discussed in the Boone Declaration during prosecution (EX1002, 737-740), Alexion kept the sequence of its clinical study drug a secret, kept study participants under strict confidentiality, and maintained the physical antibody supplies under lock and key with strictly limited access. (*See* Section II.E.)

Moreover, a POSA attempting to determine the sequence of “eculizumab” as described in Bell would have followed that publication’s reference to Thomas and arrived at the IgG4 antibody that Thomas described—an antibody having a very different sequence than the one recited in the ’504 patent. (See Section III.A.1.)

Alexion’s so-called admissions that the claimed sequence was known before 2007 are neither here nor there. What matters is what the art actually taught, not whether it was correct or what Alexion inadvertently incorrectly said about it. The fact is that as of March 15, 2007, the art consistently taught that the sequence of eculizumab had an IgG4, **not** the claimed sequence.

With respect to Bell, in contrast to the facts of *In re Crish*, 393 F.3d 1325 (Fed. Cir. 2004) (“*Crish*”), “eculizumab” was not a “known” antibody for which the sequence could have been determined. See *Endo*, 894 F.3d at 1378-79. As the Boone Declaration explained, the identity of the sequence and composition of the antibody product used in the clinical trials published as Bell was confidential. No one outside of Alexion (or those bound in confidentiality to Alexion) knew the actual sequence of “eculizumab,” nor could they have obtained the antibody for sequencing. Neither Samsung nor this Panel have disputed that fact. Moreover, a POSA attempting to determine the sequence of “eculizumab” as described in Bell would have followed those publications’ references to Thomas and arrived at the

IgG4 antibody that Thomas described—an antibody having a very different sequence than the one recited in the '504 patent. (See Section III.A.1.)

On one hand the Board admits that, here, the prior art discloses eculizumab, but possibly not *its specific sequence*, and on the other, analogizes to *Crish* for “claiming a known material.” (Paper No. 9, 50.) The Board then continues to use circular logic while analyzing *Crish*, concluding that “the prior art discloses the claimed antibody, eculizumab, and how to construct it, even if there may have been *some confusion by those in the field* over precisely the structure of the antibody’s heavy chain (i.e., IgG4 or IgG2/G4).” (Paper No. 9, 51-52.) Here, the Board incorrectly downplays the impact of the art’s teaching towards IgG4, and mistakes an obviousness argument for an anticipation argument.

Further, Alexion’s “contribution to the art” goes well beyond that of *Crish*, because the novel, hybrid IgG2/IgG4 antibody was not already known and used in the art. The Board also attempts to analogize to *Crish* via the common ownership and named inventors across the '504 patent and the prior art, but this point is legally irrelevant and has no place in an anticipation inquiry. (Paper No. 9, 51.) Accordingly, *Crish* is distinguishable on the facts and does not merit a finding that Bell inherently anticipates the claims of the '504 patent.

Likewise, Samsung and the Board, misapply *Nichols Institute Diagnostics, Inc. v. Scantibodies Clinical Laboratory, Inc.*, 195 F. App'x 947 (Fed. Cir. 2006) (“*Nichols*”). In *Nichols*, the Federal Circuit found a claim to an antibody that selectively binds a peptide of hPTH with one of six peptide sequences was inherently anticipated by a prior art abstract that disclosed an antibody that “necessarily has the claimed binding properties.” *Nichols*, 195 F. App'x at 952. Here, however, the “eculizumab” antibody referenced in Samsung’s prior art cannot “**necessarily** [have] the claimed [sequence]” if the sequence was unknown and the prior art principally points to Thomas, which discloses a very different antibody. Moreover, despite the Board’s finding that “there is no dispute” (as in *Nichols*) that the prior art antibody is the claimed antibody, Patent Owner has consistently shown that the antibody described in the prior art is **not** the claimed antibody. (See, e.g., ALXN2022 ¶¶ 174-184.) Thus, *Nichols* also fails to support a finding of inherent anticipation of the ’504 patent claims.

As Samsung cannot show the presence of all of the elements of claims 1-5 and 7-10 in Bell, Ground 5 fails to show invalidity of the ’504 patent’s claims. A decision finding invalidity on this Ground would be error by the Board based on a clear misapplication of the law of anticipation.

F. The Objective Indicia of Non-Obviousness Support Validity

Samsung's denial of the existence of secondary considerations of non-obviousness is just a rehashing of its prior art obviousness arguments (Petition, 62-65), and the Board's premature dismissal of Patent Owner's secondary considerations is improper. In short, Samsung argues, and the Board incorrectly accepts, that the strong indicia of non-obviousness here don't count because eculizumab and its sequence were already known in the art. But that is, of course, circular. There is no dispute that the indicia of non-obviousness here are due to the specific composition of the uniquely-engineered, claimed sequences and that there is nexus between those sequences and those indicia. Such minimal examination of Patent Owner's secondary considerations, would be impermissible error if carried through to final decision.

Objective indicia of non-obviousness, including commercial success, long-felt but unmet need, and industry praise, further support the validity of the '504 patent claims. *See, e.g., LEO Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). The indicia of non-obviousness "are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements." *Id.* Such evidence must receive fair and full consideration. *Graham*, 383 U.S. at 36.

SOLIRIS[®], the commercial embodiment of the '504 patent, is a resounding commercial success—having generated substantial sales in the relevant market. *See, e.g., J.T. Eaton & Co., Inc. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *Neupak, Inc. v. Ideal Mfg. Sales Corp.*, 41 Fed. App'x 435, 440 (Fed. Cir. 2002). In the United States, the annual net product sales for SOLIRIS[®] exceeded \$1 billion for 2015-17 for all indications, continuing to grow to over \$1.588 billion in 2018 (a 28.6% increase from 2017). (ALXN2018, 70.) The outstanding economic performance of SOLIRIS[®] has a direct nexus to the patented features of the '504 patent, which claims the uniquely-engineered, non-naturally occurring antibody responsible for the drug's clinical (and therefore commercial) success as a treatment for PNH. *See, e.g., Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392-93 (Fed. Cir. 1988).

The introduction of SOLIRIS[®] also fulfilled a long-felt, unmet need in the market, as the first FDA-approved treatment to reduce hemolysis in patients with PNH—demonstrated by the FDA and the EU granting SOLIRIS[®] “orphan drug” status for PNH. (ALXN2019, 1270.) *See, e.g., Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994, 997-998 (Fed. Cir. 2009). SOLIRIS[®] 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.)

Samsung and the Board improperly rely on *Ormco Corp v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006) in circular fashion to rebut the presumption of nexus between SOLIRIS[®] and the claimed invention. The unique claimed sequences are “the feature that creates the commercial success,” and contrary to the arguments in Samsung’s Grounds, the claimed sequences were novel and non-obvious at the time of the invention.

Samsung also argues that its intent to develop a biosimilar copy of SOLIRIS[®] should not count as secondary evidence of non-obviousness because it is required by statute and regulation to make a product highly similar to the reference product. (Petition, 65.) This is not so. Samsung, Amgen, and at least two other sophisticated pharmaceutical companies could have chosen to develop biosimilars of any of hundreds of other biologic products. (*See, e.g.,* clinicaltrials.gov.) Instead, they chose to copy SOLIRIS[®]. That Samsung has 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. Moreover, *Adapt Pharma*

Operations Ltd. v. Teva Pharms. USA, Inc., 25 F.4th 1354 (Fed. Cir. 2022), an ANDA case which Samsung and the Board both rely on, is less relevant in the context of antibodies, where market competitors may be choose to innovate structurally distinct products that have similar functional properties. *Accord Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023).

VI. **CONCLUSION**

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

Respectfully submitted,

CAHILL, GORDON & REINDEL LLP

/Gerald J. Flattmann, Jr./

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

Date: March 12, 2024
32 Old Slip
New York, NY 10005
(212) 701-3645
gflattmann@cahill.com

CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing **PATENT OWNER'S RESPONSE** and **EXHIBITS ALXN2006, 2014, 2023, 2025, 2028–2031, 2033–2040, 2042–2047, 2049–2055, 2075, 2079–2086, 2088–2091, 2104–2107** were served via electronic mail on March 12, 2024, in their entirety on the following:

Names

Michelle S. Rhyu (Reg. No. 41,268)
rhyums@cooley.com
Daniel J. Knauss (Reg. No. 56,393)
dknauss@cooley.com
Cooley LLP
1299 Pennsylvania Ave. NW, Suite 700
Washington DC 20004

CAHILL GORDON & REINDEL LLP

/Gerald J. Flattmann, Jr./

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

Date: March 12, 2024
32 Old Slip
New York, NY 10005
(212) 701-3645
gflattmann@cahill.com

CERTIFICATION OF WORD COUNT

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CAHILL GORDON & REINDEL LLP

/Gerald J. Flattmann, Jr./

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

Date: March 12, 2024
32 Old Slip
New York, NY 10005
(212) 701-3645