

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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SAMSUNG BIOEPIS CO., LTD.,  
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.  
Patent Owner.

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

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**PATENT OWNER'S PRELIMINARY RESPONSE  
UNDER 37 C.F.R § 42.107**

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**EXHIBIT LIST<sup>1</sup>**

| <b>Exhibit No.</b>  | <b>Description of Document</b>                                                                                                                                                                                        |
|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2001 to 2004</b> | <i>Intentionally left blank</i>                                                                                                                                                                                       |
| <b>2005</b>         | SOLIRIS® Label                                                                                                                                                                                                        |
| <b>2006</b>         | <i>Intentionally left blank</i>                                                                                                                                                                                       |
| <b>2007</b>         | Janeway and Travers, <i>Immunobiology: The Immune System in Health and Disease</i> (Garland Science, 6thed. (2005))                                                                                                   |
| <b>2008</b>         | McCloskey <i>et al.</i> , Human Constant Regions Influence the Antibody Binding Characteristics of Mouse-Human Chimeric IgG Subclasses, IMMUNOLOGY, 88: 169-173 (1996)                                                |
| <b>2009</b>         | 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) |
| <b>2010</b>         | Janda <i>et al.</i> , Ig Constant Region Effects on Variable Region Structure and Function, FRONT. MICROBIOL., 7(22): 1-10 (2016)                                                                                     |
| <b>2011</b>         | Pritsch <i>et al.</i> , Can Immunoglobulin CH1 Constant Region Domain Modulate Antigen Binding Affinity of Antibodies?, J. CLIN. INVEST., 98(10): 2235-43 (1996)                                                      |

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<sup>1</sup> 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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| <b>2012</b> | Pritsch <i>et al.</i> , Can Isotype Switch Modulate Antigen-Binding Affinity and Influence Clonal Selection?, EUR. J. IMMUNOL., 30: 3387-95 (2000)                                                                                                                                                                                                                                                                                                   |
| <b>2013</b> | McLean <i>et al.</i> , Isotype Can Affect the Fine Specificity of an Antibody for a Polysaccharide Antigen, J. OF IMMUNOLOGY, 169: 1379–86 (2002)                                                                                                                                                                                                                                                                                                    |
| <b>2014</b> | <i>Intentionally left blank</i>                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>2015</b> | Radbruch, <i>et al.</i> , Drastic Change in Idiotypic but Not Antigen-Binding Specificity of an Antibody by a Single Amino-Acid Substitution, NATURE, 315(6): 506-508 (1985)                                                                                                                                                                                                                                                                         |
| <b>2016</b> | U.S. Patent No. 7,482,435, issued to Bowdish <i>et al.</i>                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>2017</b> | Hawkins <i>et al.</i> , The Contribution of Contact and Non-contact Residues of Antibody in the Affinity of Biding to Antigen: The Interaction of Mutant D1.3 Antibodies with Lysozyme, J. MOL. BIO., 234: 958-964 (1993)                                                                                                                                                                                                                            |
| <b>2018</b> | Hawkins <i>et al.</i> , The Contribution of Contact and Non-contact Residues of Antibody in the Affinity of Biding to Antigen: The Interaction of Mutant D1.3 Antibodies with Lysozyme, J. MOL. BIO., 234: 958-964 (1993)                                                                                                                                                                                                                            |
| <b>2019</b> | Ricklin & Lambris, Complement-Targeted Therapeutics, NATURE BIOTECHNOLOGY, 25(11); 1265-1275 (2007)                                                                                                                                                                                                                                                                                                                                                  |
| <b>2020</b> | Alexion Press Release, Alexion’s Soliris® Receives 2008 Prix Galien USA Award for Best Biotechnology Product, September 25, 2008, available at <a href="https://news.alexion.com/press-release/company-news/alexions-soliris-receives-2008-prix-galien-usa-award-best-biotechnology-p">https://news.alexion.com/press-release/company-news/alexions-soliris-receives-2008-prix-galien-usa-award-best-biotechnology-p</a> (last visited May 15, 2019) |

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| <b>2021</b>                 | BusinessWire, Alexion's Soliris® Receives 2009 Prix Galien France for Most Innovative Drug for Rare Disease, June 10, 2009, available at <a href="https://www.businesswire.com/news/home/20090610005826/en/Alexions-Soliris®-Receives-2009-Prix-Galien-France">https://www.businesswire.com/news/home/20090610005826/en/Alexions-Soliris®-Receives-2009-Prix-Galien-France</a> (last visited May 15, 2019) |
| <b>2022</b>                 | Declaration of Arturo Casadevall. M.D., Ph.D.                                                                                                                                                                                                                                                                                                                                                              |
| <b>2023</b>                 | <i>Intentionally left blank/Reserved</i>                                                                                                                                                                                                                                                                                                                                                                   |
| <b>2024</b>                 | Declaration of Bernhardt L. Trout, Ph.D.                                                                                                                                                                                                                                                                                                                                                                   |
| <b>2025</b>                 | <i>Intentionally left blank/Reserved</i>                                                                                                                                                                                                                                                                                                                                                                   |
| <b>2026</b>                 | Declaration of Michel C. Nussenzweig, M.D., Ph.D.                                                                                                                                                                                                                                                                                                                                                          |
| <b>2027<br/>to<br/>2097</b> | <i>Intentionally left blank/Reserved</i>                                                                                                                                                                                                                                                                                                                                                                   |
| <b>2098</b>                 | Harlow and Lane, Chapter 2:Antibody Molecules, in <i>Antibodies, A Laboratory Manual</i> (1988)                                                                                                                                                                                                                                                                                                            |
| <b>2099</b>                 | <i>Intentionally left blank</i>                                                                                                                                                                                                                                                                                                                                                                            |
| <b>2100</b>                 | Rother, R., <i>et al.</i> , "Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria," <i>Nature Biotechnology</i> 25: 1256-1264 (2007)                                                                                                                                                                                                  |
| <b>2101</b>                 | Prosecution History for U.S. Patent No. 9,718,880 B2, submitted by Petitioner Samsung BioEpis Co., Ltd. in IPR2023-00998 as EX1002                                                                                                                                                                                                                                                                         |
| <b>2102</b>                 | Prosecution History for U.S. Patent No. 10,590,189 B2, submitted by Petitioner Samsung BioEpis Co., Ltd. in IPR2023-01069 as EX1002                                                                                                                                                                                                                                                                        |
| <b>2103</b>                 | <i>Intentionally left blank</i>                                                                                                                                                                                                                                                                                                                                                                            |

**I. INTRODUCTION**

Alexion provides the following Preliminary Response to Samsung's petition seeking review of claims 1-10 of Alexion's U.S. Patent No. 9,718,504 ("the '504 patent"). The Board should deny Samsung's petition under 35 U.S.C. § 325(d) because Samsung's prior art and Grounds are duplicative of the art and arguments that were already before this Office during the prosecution of the '504 patent, in prior IPRs brought by Amgen, and during prosecution of similar claims subsequently granted by the Examiners in child patents to the '504 patent. Further, each of Samsung's Grounds is fatally flawed by hindsight and fails to prove that the challenged claims are unpatentable.

Samsung's petition comes far too late—long after this Board considered “the same or substantially the same prior art or arguments” in three IPR petitions brought by Amgen in 2019,<sup>2</sup> and after the Examiners yet again considered all of that art and arguments as well as the entire Amgen IPR record before once again allowing claims covering the unique sequence of SOLIRIS® in Alexion's U.S.

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<sup>2</sup> IPR2019-00739 (the '504 patent); IPR2019-00740 (U.S. Patent No. 9,718,880 (“the '880 patent”); IPR2019-00741 (U.S. Patent No. 9,732,149 (“the '149 patent”).

Patent Nos. 10,590,189 (“the ’189 patent”) and 10,703,809 (“the ’809 patent”), child patents to the ’504 patent. Despite working on its proposed biosimilar version of SOLIRIS<sup>®</sup> since as early as 2018<sup>3</sup>, beginning comparative trials in the U.S. in 2019,<sup>4</sup> and being fully aware of Amgen’s earlier petitions, Samsung waited over four years, and after the PTO had examined the same universe of arguments and prior art yet again in two separate child applications, to bring these stale and redundant challenges. Institution should, therefore, be denied under Sections 314(a) and 325(d).

Further, each of Samsung’s five Grounds is based on an erroneous premise—that a person of ordinary skill in the art (“POSA”) would have known the specific amino acid sequence of the uniquely-engineered antibody recited in the claims of the ’504 patent and commercialized as Alexion’s groundbreaking orphan disease therapy known today as SOLIRIS<sup>®</sup>. Before March 15, 2007, the priority date of the ’504 patent, however, the unique amino acid sequence of SOLIRIS<sup>®</sup>

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<sup>3</sup> See <https://www.biopharma-reporter.com/Article/2018/10/30/Samsung-Bioepis-targets-Soliris-market-with-many-more-candidates-in-pipeline>.

<sup>4</sup> See <https://clinicaltrials.gov/study/NCT04058158?cond=PNH%20&intr=eculizumab&term=samsung&rank=4&tab=history>.

was not publicly known or disclosed in the prior art. Samsung's arguments to the contrary are concocted from prior art that the PTO already considered multiple times, and that Samsung and its declarant, Dr. Ravetch, deliberately selected and combined using hindsight knowledge. The PTO presumably agrees that Samsung's arguments are flawed, as it rejected the substantially similar hindsight arguments Amgen put forth years ago when it allowed two similar claim sets to grant despite being presented with those arguments in the prosecutions of the child patent applications.

As previously demonstrated in the Declaration of Dr. Arturo Casadevall, submitted in IPR2019-00739 (*see, e.g.*, ALXN2022, ¶¶ 139-173, 192-262),<sup>5</sup> the

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<sup>5</sup> The Declaration of Dr. Arturo Casadevall, a renowned expert in the field of immunology and antibodies, was submitted in IPR2019-00739 in support of Patent Owner 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 in this Patent Owner Preliminary Response. Alexion reserves the right to submit one or more expert declarations specifically directed to Samsung's petition if any Grounds are instituted.

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.

As Samsung fails to show that any of the challenged claims are unpatentable, Samsung’s request for institution must be denied. *See* 35 U.S.C. § 314(a); 37 C.F.R. § 42.108(c).

## **II. BACKGROUND**

### **A. SOLIRIS® and Its Use to Treat PNH**

The challenged claims of the ’504 patent generally cover methods of treating paroxysmal nocturnal hemoglobinuria (“PNH”) comprising administering pharmaceutical compositions of a non-naturally occurring, uniquely-engineered humanized antibody developed by Alexion and marketed as SOLIRIS®. The FDA approved SOLIRIS® on March 16, 2007, as the first approved therapy to reduce hemolysis in patients with PNH. (*See* ALXN2100 at 1256; ALXN2005 at 1.)

SOLIRIS® works by binding with high “affinity” (*i.e.*, tightness) and “specificity” (*i.e.*, directed to a single antigen) to the human protein “C5,” a key component of the complement pathway. Without SOLIRIS® treatment, the body naturally cleaves C5 into components “C5a” and “C5b,” which leads 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 at 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 at 110; ALXN2098 at 5-7.)

Each of the heavy and light chain polypeptides can be divided into a “variable” region, where the antigen binds, and a “constant” region, which may interact with other components of the immune system. (ALXN2007 at 105-06.) The variable region is comprised of a portion of the light chains (“V<sub>L</sub>”) and a portion of the heavy chains (“V<sub>H</sub>”). (ALXN2007 at 105-06.) Likewise, the constant region is comprised of a portion of the light chains (“C<sub>L</sub>”) and a portion of the heavy chains (“C<sub>H</sub>”). (ALXN2007 at 105-06.) The variable region of each of the four chains includes three “complementarity determining regions” (“CDRs”), which together directly interact with a single epitope on a specific antigen.

(ALXN2098 at 9.) Portions of the variable region flanking the CDRs are termed “framework” regions. (EX1044 at 6.)

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 at 105; ALXN2098 at 4; EX1044 at 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  $C_{H3}$ .

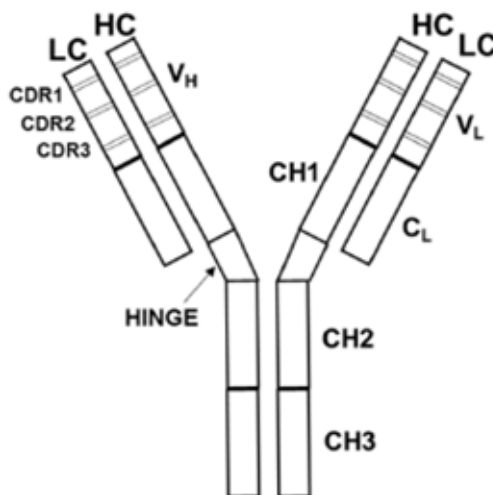


**Figure 1:** Basic structure of an IgG antibody

(See ALXN2022, ¶¶ 63-69.)

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

(ALXN2007 at 105; EX1044 at 5.) The various isotypes differ structurally in the

amino acid sequences of their C<sub>H</sub> regions, the number and location of their disulfide bonds, and the lengths of their “hinge” regions. (See, *e.g.*, ALXN2008 at 172; see also ALXN2009 at 13924; EX1044 at 5.) As of March 15, 2007, humanized monoclonal antibodies approved by the FDA were predominantly of the naturally occurring IgG1 or IgG4 isotypes, and all used one of the naturally occurring IgG constant regions. (See, *e.g.*, EX1044 at 2-4, Table 1; ALXN2022, ¶ 81.)

**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 clinical trials to be safe and effective for the treatment of PNH. (EX1011 at 552, 558; EX1013 at 2559, 2564; EX1014 at 1239, 1241-1242.) But a POSA at that time would **not** have known that “eculizumab” had the sequence claimed in the ’504 patent, including the uniquely-engineered C<sub>H</sub> region reflected in “SEQ ID NO: 2.” Rather, the literature taught a POSA that “eculizumab” contained an “**IgG4**” C<sub>H</sub> region that is **very different** from “SEQ ID NO: 2.”

Specifically, the literature as of March 15, 2007 consistently directed a POSA to read Thomas (EX1010) for the structure and sequence of the

“eculizumab” antibody shown to block C5 cleavage and to safely and effectively treat PNH. (See, e.g., EX1011 at 553 (citing EX1010 (Ref. No. 15)); EX1013 at 2559 (citing EX1010 (Ref. No. 9)); EX1014 at 1234 (citing EX1010 (Ref. No. 13)); EX1007, ¶ [0052] (citing EX1010); EX1023 at 1018 (citing EX1010 (Ref. No. [258884])).) Thomas, in turn, described the design and testing of a humanized anti-C5 antibody (termed “humanized 5G1.1” or “h5G1.1”) featuring an “***IgG4***” C<sub>H</sub> region, which was selected because the IgG4 isotype was thought to avoid activating human complement. (EX1010 at 1396, 1399.<sup>6</sup>) 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 blocking C5 cleavage and preventing lysis of blood cells due to complement activity. (EX1010 at 1396; ALXN2022, ¶¶ 123-124.)

**D. Structure and Sequence of SOLIRIS<sup>®</sup>,  
Which 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<sup>®</sup> has the amino acid sequence recited in the ’504 patent’s

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<sup>6</sup> Unless otherwise noted, all emphasis is added, and all internal citations and quotation marks are omitted.

claims, 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 prevent C5 cleavage or would safely and effectively treat conditions such as PNH.

Today, but **not** before March 15, 2007, it is known that SOLIRIS<sup>®</sup> is a unique antibody that is **very different** from the humanized IgG4 antibody described in Thomas. As understood today, but not as of March 15, 2007, the heavy chain of SOLIRIS<sup>®</sup> (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. (ALXN1033 at 1257-1258.) Notably, SOLIRIS<sup>®</sup> was the first FDA-approved product containing Alexion’s uniquely-engineered C<sub>H</sub> 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 would be safe or effective for human therapeutic use.

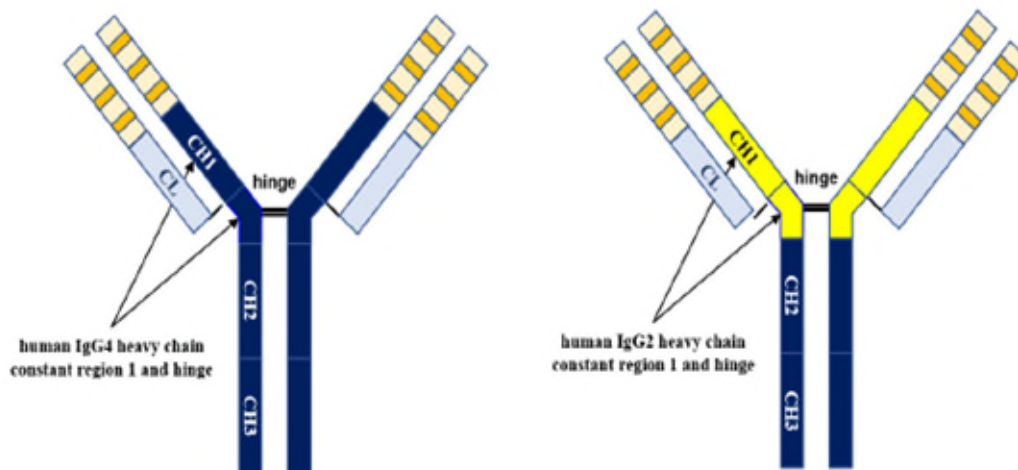
The structure of eculizumab that is known today and claimed in the ’504 patent is shown below compared to Thomas’s IgG4 isotype antibody, which the literature before March 15, 2007 taught a POSA was “eculizumab.” Unlike

Thomas's IgG4 antibody, the claimed antibody uses the C<sub>H</sub>1 and “hinge” regions of IgG2, thereby providing a very different antibody than that described in Thomas.

**Figure 2:**

**Left –** Structure of the IgG4 isotype antibody referenced to as “eculizumab” in the literature as of March 15, 2007

**Right** – Structure of SOLIRIS<sup>®</sup>, having a non-naturally occurring, protein-engineered isotype



(See ALXN2022, ¶¶ 135-137.)

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.” That ignores the overwhelming evidence that directed a POSA to look to Thomas for the structure of “eculizumab.” (See Section IV.A.1.) 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 over the consistent, clear statements in earlier and later publications that expressly identified “eculizumab” as Thomas’s IgG4 antibody.

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 IV.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.)

Nothing in Tacken contradicted the consistent teaching of the prior art **as a whole** that “eculizumab” had an IgG4 constant region. In a single sentence identifying an “isotype control antibody” for use in studies of the “hD1” antibody, Tacken cites to **Thomas** (Ref. No. 19) and states:

An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals) containing the same IgG2/IgG4

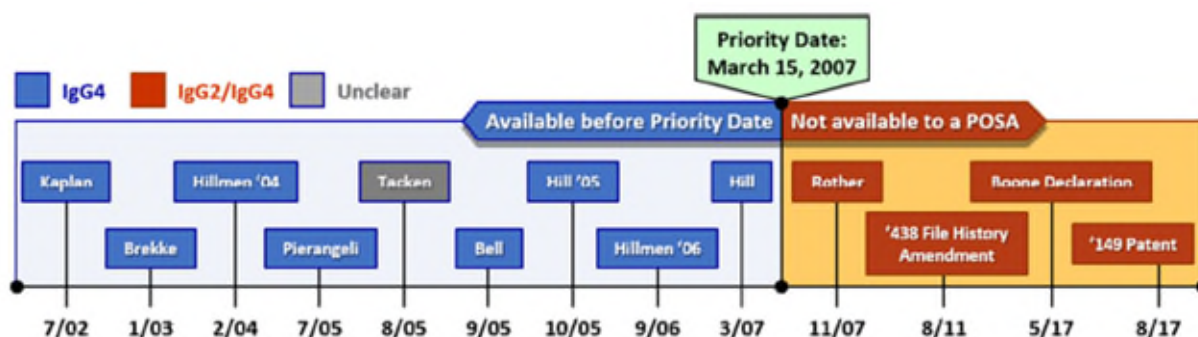
constant region, is specific for the human terminal complement protein C5.<sup>(19)</sup>

(EX1008, 1279.) A POSA reading that isolated statement would not have been dissuaded from the consistent, clear teaching in the literature (both before and after Tacken’s publication, and also within Tacken itself) identifying “eculizumab” and “SOLIRIS®” as Thomas’s ***IgG4*** antibody. (See Table 1; ALXN2022, ¶¶ 141-151.) Samsung also never explains how—even if a POSA were somehow to ignore the literature and try to make an IgG2/IgG4 sequence—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.

Samsung’s myopic focus on Tacken’s isotype control antibody, to the exclusion of all other prior art information, is also not tenable because at least four prior art documents published ***after*** Tacken confirmed a POSA’s belief as of March 15, 2007 that the clinically-tested “eculizumab” antibody was Thomas’s ***IgG4*** antibody.

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. '504 Patent Overview

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

Claim 1 is the sole independent claim. Dependent claim 2 recites administration by “intravenous infusion,” and claims 3 and 8 recite certain dosing amounts or regimens. Claim 7 additionally recites that “the patient is anemic,” and

claims 9 and 10 additionally recite results regarding a “decrease in mean levels of lactate dehydrogenase.”

Dependent claims 4-6 recite additional elements further specifying the claimed pharmaceutical composition. Claim 4 recites “a single unit dosage form,” which claim 5 further provides is “a 300 mg single unit dosage form.” Claim 6 recites “a 300 mg single-use formulation” that is “30 ml of a 10 mg/ml sterile, preservative free solution.”

**F. Prosecution History of the '504 Patent and Related Applications**

In the course of the '504 patent's prosecution, as well as the prosecutions of the related '880 patent, '149 patent, '189 patent, and '809 patent, the Examiner considered the same, or substantially the same, prior art that Samsung now asserts in its petition. In doing so, the Examiner made findings undermining Samsung's positions, 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 at 1347.) The Examiner also found that SOLIRIS<sup>®</sup> 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)), as a basis for rejection, before finding the claims allowable (*see, e.g.*, EX1002 at 1036-1040, 1118-1123, 1295-1300);
- Considered Samsung's asserted reference Bell (EX1007), which Alexion submitted to the PTO (*see, e.g.*, EX1002 at 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 at 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 PCT (*see, e.g.*, EX1002 at 106; ALXN2022, ¶ 167).

Notably, during prosecution of the '504 patent and related patents, the Examiner confirmed a central fact that Samsung ignores: that Hillmen 2004 (like Bell), in describing “eculizumab” as a humanized anti-C5 antibody, cites to **Thomas** (i.e., “reference number 15” of Hillmen 2004) as “disclosing more information about eculizumab.” (EX1002 at 1038, 1118 (citing EX1011); *see also* EX1002 at 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, 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. (EX1002 at 1079-80, 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 at 1347.)

Samsung also ignores the Declaration of Dr. Loral Boone (EX1002 at 1320-27 (“the Boone Declaration”)), which the Examiner credited as showing that Alexion’s clinical studies of the claimed antibody, including those published in Bell and Hillmen 2004, did not disclose its sequence or render it publicly accessible. (EX1002 at 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 at 1347, 1324-27 at ¶¶ 6-13.) While, as Dr. Boone explained, it is known *today* that SOLIRIS® as used in these studies had the claimed sequence (EX1002 at 1324, ¶ 6), a POSA as of March 15, 2007 would have only been guided by what was reported in the published literature, *i.e.*, the teaching that “eculizumab” had Thomas’s IgG4 structure.

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 to issue. (EX1002 at 1347-48.)

III. **INSTITUTION SHOULD BE DENIED UNDER 35 U.S.C. §§ 325(D) AND 314(A)**

Samsung’s Petition raises the “same or substantially the same prior art or arguments” previously presented to the PTO and should therefore be denied under Section 325(d):

| <b>References Considered in Prosecution Histories (PH)</b>                       |                           |                         |         |         |
|----------------------------------------------------------------------------------|---------------------------|-------------------------|---------|---------|
|                                                                                  | '504 PH                   | Amgen IPRs <sup>†</sup> | '809 PH | '189 PH |
| Bowdish                                                                          | '435 patent <sup>7</sup>  | ✓                       | ✓       | ✓       |
| Evans                                                                            | ✓                         | ✓                       | ✓       | ✓       |
| Mueller PCT/1997                                                                 | Mueller 1997 <sup>8</sup> | ✓                       | ✓       | ✓       |
| Tacke                                                                            |                           | ✓                       | ✓       | ✓       |
| Bell/Hillmen/Hill                                                                | ✓                         | ✓                       | ✓       | ✓       |
| Wang                                                                             | ✓                         | ✓                       | ✓       | ✓       |
| <sup>†</sup> All cited in the prosecution histories of the '809 and '189 patents |                           |                         |         |         |

| <b>Arguments Considered in Prosecution Histories (PH)</b> |         |            |         |         |
|-----------------------------------------------------------|---------|------------|---------|---------|
|                                                           | '504 PH | Amgen IPRs | '809 PH | '189 PH |
| Bowdish & Evans                                           |         | ✓          | ✓       | ✓       |
| Mueller & Evans                                           |         | ✓          | ✓       | ✓       |
| Bell/Hillmen/Hill                                         | ✓       | ✓          | ✓       | ✓       |
| Bell & Wang                                               | ✓       | ✓          | ✓       | ✓       |

<sup>7</sup> The '435 patent is cumulative to Bowdish.

<sup>8</sup> Mueller 1997 is cumulative of Mueller PCT.

Examiner Rogers and Supervisory Examiner Kolker examined all five of the patents that Samsung challenges by IPR—the '880, '504, '149, '189, and '809 patents. **All** of the references that Samsung relies on in its grounds were submitted to and thoroughly considered by the Examiners in one or more of those five patent prosecutions. Plus, after Amgen filed IPRs against the '880, '504, and '149 patents, ***the entire IPR record***—including substantially similar arguments to the ones Samsung makes here—was submitted to and considered by Examiners Rogers and Kolker during the prosecutions of the '189 and '809 patents. The Examiners thus spent years becoming familiar with the same art and arguments Samsung rehashes here and yet continued to grant similar patent claims to the same novel sequence. Samsung has not shown error in the Examiners' evaluation of the art or arguments to merit a “re-do” before the Board.

**A. Legal Standards Under Section 325(d)**

The Board analyzes whether to discretionarily deny institution under Section 325(d) using the two-part framework outlined in *Adv. Bionics* along with the non-exclusive factors in *Becton. Adv. Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential); *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential in relevant part). “At bottom, this framework

reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Adv. Bionics*, Paper 6 at 9.

**B. Both Conditions of the First Part of the  
Adv. Bionics Two-Part Framework Are Met**

The first part of the *Adv. Bionics* framework requires meeting one of two conditions—that the same or substantially the same (1) art or (2) arguments were previously presented to the Office—before moving to the second part. *See Adv. Bionics*, Paper 6 at 8. Here, both conditions are met.

In the prosecutions of the ’880, ’504, and ’149 patents, each of Evans, Mueller 1997 (which is cumulative to Mueller PCT<sup>9</sup>), Thomas, Hillmen, Hill, and

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<sup>9</sup> Mueller PCT and Mueller 1997 each discuss antibodies directed against porcine VCAM protein and their use in methods related to human rejection of porcine xenotransplants. (EX1006, Abstract; EX1009, Abstract.) Both discuss the same two VCAM-blocking antibodies, 2A2 and 3F4 (EX1006, Abstract; EX1009, 11:21-34, FIGs. 4-15, ); chimeric antibodies constructed from human IgG2/G4 (EX1006, Abstract; EX1009, 8:23-26, 56-57 (human G2/G4 cDNA and amino acid sequence)), and use of “h5G1.1 CO12 HuG4” and “h5G1.1 G2/G4” antibodies as a control (EX1006 at 009, Figs.; EX1009, 12:34-38, FIGs. 11-13, and 15).

Wang was cited in an IDS and marked as considered by Examiner Rogers. This alone is sufficient to satisfy part one of the *Adv. Bionics* framework for those references. *See Adv. Bionics*, Paper 6 at 7-8 (“[previously presented art includes . . . art provided to the Office by an applicant, such as on an [IDS]]”); *Medtronic CoreValve LLC v. Speyside Med., LLC*, IPR2021-00241, Paper 9 at 23 (PTAB July 23, 2021) (noting that “[t]his factor is not so limited” to “references that are expressly included in a rejection by the examiner”); *see also Google LLC v. Valtrus Innovations Ltd.*, IPR2022-01197, Paper 18 at 16 (PTAB June 13, 2023) (gathering cases).

Additionally, counterpart references for Bowdish and Bell were cited in IDS’s during the prosecution of the ’880, ’504, and ’149 patents. *See Google LLC*, Paper 18 at 13-18 (finding part one of *Adv. Bionics* met when a reference relied on by a petitioner was not included on an IDS but its European counterpart was). For example, U.S. Patent No. 7,482,435—also published as U.S. Pub. No. 2003/0049683—is the parent patent to Bowdish and both the ’435 patent and ’683 publication were submitted in an IDS in each of the ’880, ’504, and ’149 patents. Bell was also published six different times as U.S. 2005/169921; U.S. 2010/068202; U.S. 2011/086040; U.S. 2012/308559; WO 2005/074607; and EP1720571, each of which was cited in an IDS in each of the ’880, ’504, and ’149

patents, as well as the two child patent applications. Notably, WO 2005/074607 is also cited in the specification of the challenged patents. (*See, e.g.*, '880 patent, 7:4-10.)

Further, Examiner Rogers expressly stated in many of his Office Actions that he considered each IDS submitted and, when making his rejections, noted that the references used were listed on an IDS:

| DETAILED ACTION                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Claims 1-10 pending and under consideration in the instant examination.                                                                                                                                                                                                                                                                                                                                                                                             |
| 2. The present application is being examined under the pre-AIA first to invent provisions.                                                                                                                                                                                                                                                                                                                                                                             |
| 3. Applicant's IDSs filed on 10/21/2016 and 11/4/2016 are acknowledged and have been considered.                                                                                                                                                                                                                                                                                                                                                                       |
| 4. Applicant has overcome the ODP rejections which were in the prior OA mailed on 11/4/2016 given applicant's approved TD over US Patent Application 15/148,839 (Note: applicant's has also filed an approved TD over US Patent application 15/284,015).                                                                                                                                                                                                               |
| <b>Claim Rejections - 35 USC § 102</b>                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:<br><br>A person shall be entitled to a patent unless –<br><br>(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States. |
| 6. Claims 1-2 and 7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillmen et al. (N Engl J Med 2004; 350: 552-9, IDS Ref. of 10/21/2016), as is evidenced by applicant's specification as filed at p.44 and Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996).                                                                                                                                                                      |

(*See, e.g.*, EX1002 at 1036.)

Additionally, during the subsequent prosecution of the '189 and '809 child patents, Alexion submitted the entire history of each of Amgen's IPRs against the '880, '504, and '149 patents, including all the references cited in those IPRs

including Bowdish, Evans, Bell, Tacken, and Mueller PCT as well as all expert reports and testimony, early in the prosecution to be considered by Examiners Rogers and Kolker.

The arguments were the same too. Here, Alexion uses the prosecution history of the '880 patent as exemplary of the prosecution histories of the '504 and '149 patents because the '880 patent was filed first and thus examined first. For example, in the Aug. 16, 2016 Office Action in the prosecution of the '880 patent—the first ever mailed for these five patents—Examiner Rogers rejected the pending claim as obvious over Hillmen,<sup>10</sup> Evans, and Wang, among other rejections. (ALXN2101 at 341.) In response, Alexion amended the claims to require SEQ ID NO: 2 and SEQ ID NO: 4 and argued, among other things, that, before March 15, 2007, “the complete structure of eculizumab was not disclosed in the prior art; nor was it available to the public.” (ALXN2101 at 416-418.) Examiner Rogers rejected the claims again, this time as anticipated by Hillmen as evidenced by Thomas among other rejections (ALXN2101 at 1222-23.) Examiner

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<sup>10</sup> Notably, Hillmen and Bell are cumulative to each other, as both discuss the efficacy of eculizumab in the treatment of hemolytic diseases, such as PNH.

Rogers also requested additional information under “Rule 105” noting how “the extensive number of both patent literature and NPL documents as well as clinical trials indicates that eculizumab was widespread and well-known.” (ALXN2101 at 1223, 1227-29.) When responding, Alexion provided the requested information and argued, *inter alia*, that “none of the cited references teach the sequence of eculizumab, let alone its unique, non-naturally occurring, protein-engineered full heavy chain.” (ALXN2101 at 1370, 1374-380.) Examiner Rogers allowed the claims without further amendment.

A similar pattern played out in the prosecution of the other four patents. For example, the prosecution history summary for the ’504 patent provided above reveals the similarities between that prosecution and the prosecution of the ’880 patent. (See Section II.F.) And a review of the ’504 prosecution history shows that Examiner Rogers made similar rejections as in the ’880 prosecution (ALXN2101 at 837-844; 1034-1040; 1116-1127) and that Alexion made similar arguments in response (*id.* at 980-986; 1076-1082; 1292-1302).

Moreover, during the ’189 patent’s prosecution, Examiner Rogers rejected the then-pending claims over a combination of Hillmen, Evans, Wang, and Bowdish, and argued that one could “substitute Bowdish’s TPO mimic [sic] amino acid sequence . . . with Evan’s [sic] CDR3 5G1.1 eculizumab amino acid

sequence.” (ALXN2102 at 11380.) Alexion overcame that rejection using the same arguments presented here and Examiner Rogers allowed the claims without substantive amendments. Thus, the Examiners fully considered the art and same types of anticipation and obviousness arguments Samsung makes again.

Samsung’s petition retreads the same ground already covered by the Examiners. For example, Samsung relies on Evans and Bowdish in the same way that Examiner Rogers did in the prosecution of the ’189 patent. (*Compare* ALXN2102 at 11380 *with* Petition at 30-31.) Additionally, Samsung relies on Bell (EX1007) in the same way Examiner Rogers did in a rejection during the prosecution of the ’189 patent (*i.e.*, for treatment of PNH using an anti-C5 antibody such as h5G1.1). (*Compare* ALXN2102 at 11382 *with* Petition at 29.) ***Moreover, Samsung fails to account for the fact that the entire history of the Amgen IPRs was submitted to Examiner Rogers during the prosecution of the ’189 and ’809 patents, including Amgen’s identical arguments regarding Tackn.***

Further, the same basic combinations Samsung uses here to argue that the claimed sequences were obvious—(1) Bowdish and Evans (Grounds 1 and 2); and (2) Mueller and Evans (Grounds 3 and 4)—were used in Amgen’s IPRs for the same purpose, and hence, those same combinations and arguments were before the

Examiners during the prosecution of the '189 and '809 patents. (*See, e.g.*, ALXN2022, ¶¶ 192-262.) Here again, Samsung's grounds fail for the same reason that persuaded the Examiners: None of Samsung's references (taken alone or in the basic combinations Samsung uses) teach the unique, non-naturally occurring, protein-engineered sequence of SEQ ID NOs: 2 and 4.

**C. Samsung Has Not Shown How Examiner Rogers Erred**

The second part of the *Adv. Bionics* framework requires Samsung to demonstrate that Examiner Rogers erred in a manner material to the patentability of the challenged claims. *See Adv. Bionics*, Paper 6 at 8. Samsung has not done so.

*Becton* factors (c), (e), and (f) may be used in evaluating whether Samsung has shown a material error by the PTO. *Becton*, Paper 8 at 17-18.

**1. *Becton* Factor (c)**

During prosecution of the '504 patent and the related '880 and '149 patents, Examiner Rogers extensively considered the same art and arguments that Samsung rehashes in its Grounds 1-5.

As already noted, Examiner Rogers expressly stated in many of his office actions that he considered each IDS submitted and, when making his rejections, noted that the references used were listed on an IDS. (*See* Section III.B.)

Examiner Rogers also initialed each page of each IDS and wrote that “all references [were] considered except where lined through.” No references were lined through.

Further, the Examiners cited each of Thomas, Hillmen, and Wang in rejections during the prosecution of the '880, '504, and '149 patents, and also cited Evans in rejections during the prosecution of both the '880 and '504 patents. For example, Examiner Rogers considered and rejected the argument that the claimed antibody sequence was disclosed by Hillmen after Alexion explained how Hillmen pointed a POSA to the IgG4 antibody of Thomas for the structure of “eculizumab.” (See Section II.F.) Samsung’s Ground 5, relying on Bell in place of Hillmen (as do Grounds 1-4) fails for the same reason: Bell pointed a POSA to Thomas for the structure of “eculizumab.” (See *e.g.*, Section II.F.) The Examiner’s ultimate conclusion that none of the art taught the claimed antibody sequence is fatal to Samsung’s Grounds 1-5.

The Examiner of the '880 patent also thoroughly considered Evans (Grounds 1-4) and Wang (Grounds 2 and 4), and reviewed other references pertaining directly to Samsung’s Grounds, including Bell (Grounds 1-5); U.S. Patent No. 7,482,435, which is cumulative of Bowdish (Grounds 1-2); and Mueller 1997, which is cumulative of Mueller PCT (Grounds 3-4). After having reviewed all of

those references, the Examiner concluded that nothing in the art taught or suggested an anti-C5 antibody with the specific sequence recited in claims 1-3. (See Section II.F.)

The references relied on by Samsung were then thoroughly considered once again in the prosecutions of the '189 and '809 patents, child patents of the '880, '149, and '504 patents, that claim the same uniquely-engineered sequence. In fact, the entire history, including arguments, expert declarations and testimony, of the Amgen IPRs was submitted for Examiner Rogers' consideration during the prosecution of the '189 and '809 patents. See *BMW of N. Am., LLC v. Stragent, LLC*, IPR2021-00426, Paper 13 at 8-18 (PTAB July 19, 2021) (denying institution under 325(d) where "Patent Owner advised the Patent Office of the Prior IPR" in a child application). Examiner Rogers' rejections of the then-pending claims of the '189 patent over Hillmen, Evans, Wang, Bowdish, and Bell were clearly influenced by the arguments made in the Amgen IPRs. For example, Examiner Rogers presented a sequence alignment of Bowdish's SEQ ID NOS: 67 and 69 with the claimed SEQ ID NOS: 2 and 4, respectively, and reiterated the arguments Amgen made regarding Bowdish; Samsung recycles those same arguments here. (See ALXN2102 at 11378-79.)

## **2. *Becton Factor (e)***

Samsung faults Alexion for mischaracterizing the prior art and misleading Examiner Rogers into supposedly committing factual and legal error. (Petition at 62-72.) But Samsung rests these arguments on the same flawed, stretched, and hindsight-driven characterization of the art that dooms its Grounds. At bottom, Samsung's arguments amount to nothing more than unsupported accusations that Alexion misled both Examiners Rogers and Kolker and that those Examiners did their jobs poorly. The record, however, speaks for itself and shows Alexion's efforts to disclose all known information, and to the Examiners' thorough job well done.

Samsung's argument that Examiner Rogers overlooked Bell's and Bowdish's antibody sequence information by focusing only on Evans and Thomas is conclusory and unsupported. (Petition at 62.) It ignores that Examiner Rogers used both Bell and Bowdish in rejections during the prosecution of the '189 patent and, in the Notice of Allowance, referred to Evans as "[t]he closest prior art" and Bowdish as "[t]he secondary reference," referring specifically to Bowdish's antibody sequence information. (See ALXN2102 at 14874.)

Nor does Samsung offer evidence for how Examiner Rogers "failed to appreciate" Tacken, Mueller PCT, and Bowdish. (Petition at 69.) In fact, the

opposite is true with respect to Mueller PCT and Bowdish because each was cited in an IDS as a cumulative reference (Mueller 1997) or counterpart (U.S. Patent No. 7,482,435) and marked as considered by Examiner Rogers. Plus, Bowdish was used in a rejection during the prosecution of the '189 patent. (*See, e.g.,* ALXN2102 at 11377.) Further, even if Examiner Rogers did not consider Tacken—and there is no evidence that he did not, as he clearly considered the Amgen IPRs that use Tacken in the same way Samsung does—Tacken discloses the same information as other references that were considered because it led a POSA to Thomas's IgG4 sequence.

Samsung's attempt to lessen the impact of the '189 patent's prosecution also falls flat because one undisputed fact remains: ***the entire record of three instituted IPRs for three patents that Examiners Rogers and Kolker themselves already thoroughly examined was provided to them during the prosecution of two follow-on child applications that claim the same SEQ ID NOs: 2 and 4 as the parents, and, after another review of the art, Examiners Rogers and Kolker granted those two follow-on applications as the '189 and '809 patents.***

With respect to Samsung's Error 1, Samsung presents no evidence that the Examiners did not "appreciate Tacken's and Mueller PCT's disclosure" other than an observation that those references were not cited in an Office Action or Notice of

Allowance. It is equally plausible that the Examiners fully considered Tackén's and Mueller PCT's disclosures, as well as Alexion's arguments against the use of those references in the Amgen IPR record. Apple's reliance on *SEVEN Networks* is inapplicable. *Apple Inc. v. SEVEN Networks, LLC*, IPR2020-00285, Paper 10 (PTAB July 28, 2020). First, *SEVEN Networks* is neither precedential nor informative. Second, it is distinguishable on the facts. In *SEVEN Networks*, the Board found that the continuation application was separate and distinct from the challenged patent while, here, the majority of Samsung's arguments focus on SEQ ID NOS: 2 and 4, which are recited in the claims of all challenged patents. Further, the Board found that none of the references used in the IPR petition were included in an IDS during prosecution of the challenged patent and there was no indication the Examiner considered them. As discussed above, the opposite is true here.

It is evident that Examiner Rogers considered the Amgen IPRs because his rejections changed (he cited Bowdish and Bell in rejections in the '189 patent) and his reasons for allowance changed (he cited Evans as the closest prior art and Bowdish as the secondary reference). This is distinguishable from *RTI Surgical, Inc. v. LifeNet Health*, IPR2019-00573, Paper 20 (PTAB Aug. 12, 2019) where the

Board found that there was no evidence the Examiner had considered the IPR petition of a related patent.

Samsung's Errors 2, 3, and 4 rely on the same flawed and hindsight-driven arguments that Samsung relies on for its Grounds and thus should be rejected for the same reasons.

### **3. *Becton* Factor (f)**

Samsung presents no new or additional facts that have not already been submitted to and considered by Examiners Rogers and Kolker during prosecution. Samsung simply recycles the same or similar art and arguments from the patents' prosecution and the Amgen IPRs, the entire records of which were submitted to the Examiners for consideration.

Accordingly, Samsung's petition should be denied under Section 325(d). Alternatively, if the Board finds that fewer than all five Grounds meet the standard for Section 325(d), institution of Samsung's petition should still be denied in full, because institution on all five Grounds "would not be an efficient use of the Board's time and resources." *See Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Paper 7 at 41-43 (Jan. 24, 2019) (informative) (citing Section 314(a)).

IV. **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.) Yet Samsung dismisses that straightforward conclusion, and instead offers convoluted positions that require combining bits and pieces of non-analogous or irrelevant art and non-prior art statements to reach the claimed sequence.

Accordingly, Samsung errs by ignoring what the art actually taught a POSA about “eculizumab,” and instead uses hindsight to read the term “eculizumab” into other documents that never even mention that word. Samsung also does not dispute that “eculizumab”—including its sequence and structural details—was, as of March 15, 2007, a proprietary, unapproved developmental candidate that was unavailable to the public and that Alexion maintained in strict confidence.

**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<br><br>(EX1011) at 553 | ✓                                       | In reporting on a Phase II clinical trial for PNH, cites <b>Thomas</b> , 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)<br><br>at 2559    | ✓                                       | In reporting on a Phase II clinical trial for PNH, cites <b>Thomas</b> , 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<br><br>(EX1014) at 1234 | ✓                                       | In reporting on a Phase III clinical trial for PNH, cites <b>Thomas</b> , 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) at [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) at 1018 | ✓                                       | Cites <i>Thomas</i> , Ref. No. [258884], for synthesis of "[h]umanized 5G1.1," also identified as "eculizumab."                                                                                                    |
| Tacken (EX1008) at 1279 | ✓                                       | Cites <i>Thomas</i> , Ref. No. 19, as describing the antibody "h5G1.1-mAb (5G1.1, eculizumab; Alexion Pharmaceuticals)"                                                                                            |

(See ALXN2022, ¶¶ 123-124.)

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 at 9-10). And Grounds 1-4 also include Tacke's reference to Thomas, which discloses an IgG4 antibody. That alone should be basis for non-institution.

While **today** SOLIRIS<sup>®</sup> (eculizumab) is known to have the non-naturally occurring, uniquely-engineered heavy chain reflected in SEQ ID NO: 2, Samsung cannot show how a POSA as of March 15, 2007 without hindsight could have reached that conclusion. A POSA would have had no reason to doubt the consistent teachings of the literature that described "eculizumab" by pointing to Thomas's IgG4 antibody.

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

None of Samsung's cited art contradicts the consistent teaching in the literature as of March 15, 2007 that the "eculizumab" antibody shown to be clinically effective and safe for treating PNH had Thomas's IgG4 isotype structure. 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 Does Not Teach the Claimed Sequence  
of “Eculizumab” or Contradict Thomas**

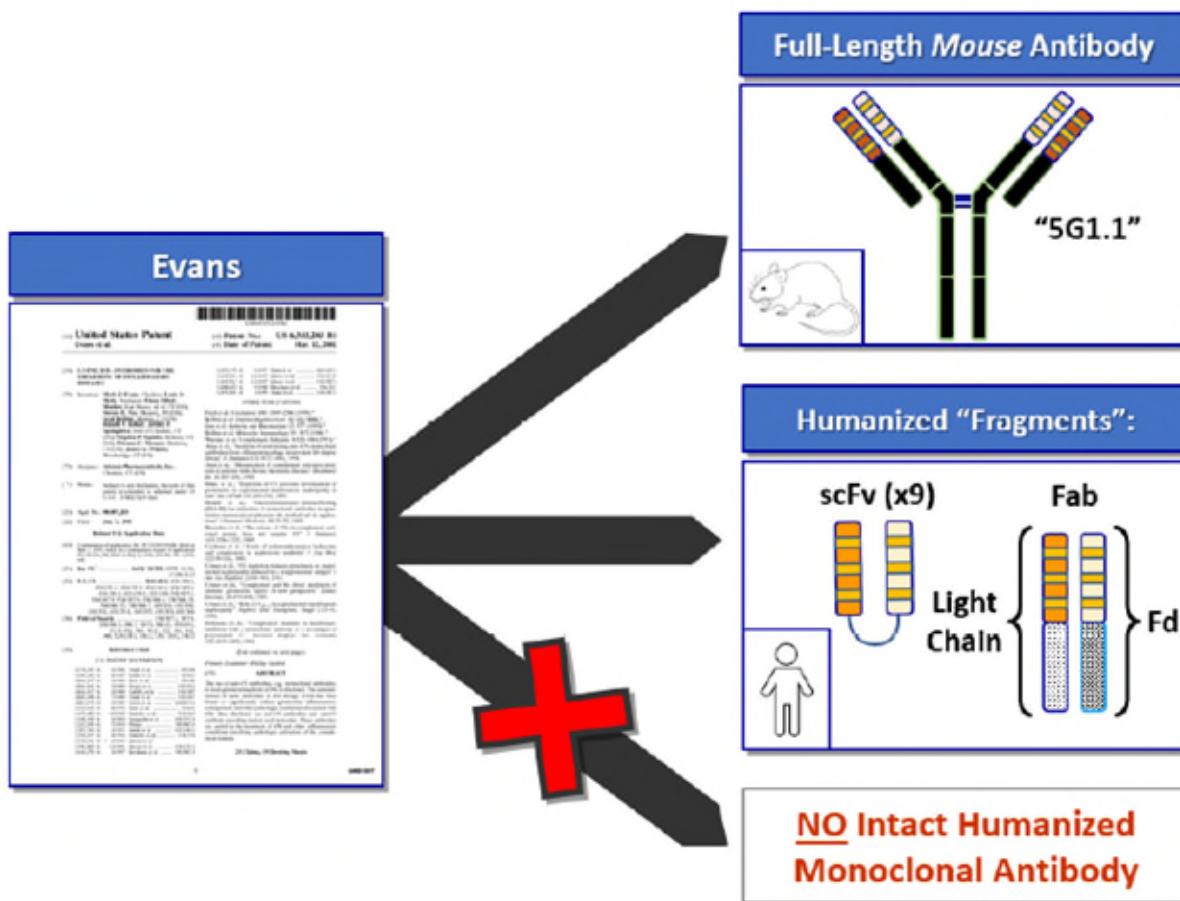
Samsung suggests that “eculizumab” was somehow disclosed or claimed by the Evans patent (*e.g.*, Petition at 20-21, 31-34), but it is undisputed that Evans neither used the term “eculizumab,” nor disclosed the heavy chain or full sequence of the claimed antibody of the ’504 patent. As Samsung concedes, Evans 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 at 43:6-45:4; Petition at 21, 30). Further, Evans only describes antibody constant regions generically (*e.g.*, stating that IgG constant regions are preferred), without identifying any specific C<sub>H</sub> region that could or

should be used. (EX1005 at 45:24-33). Nothing in Evans suggests or discloses constructing the uniquely-engineered heavy chain of the '504 patent's SEQ ID NO:

2. And a POSA as of March 15, 2007, understanding from the literature that Thomas's IgG4 isotype antibody was clinically successful, would have had no reason to do so.

Indeed, 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<sub>H</sub> region, let alone the uniquely-engineered heavy chain reflected in SEQ ID NO: 2. (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<sub>H</sub>2 and C<sub>H</sub>3) 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<sub>H</sub>1” 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**

Bowdish and Mueller are even farther afield from the problem addressed by the '504 patent's claimed invention. In contrast to the clinical study literature that cites to Thomas as describing “eculizumab,” nothing in Bowdish or Mueller taught

that the antibody recited in the claims of the '504 patent would work to prevent C5 cleavage or safely and effectively treat PNH.

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 a scaffold) with a TPO receptor (the “cMpl receptor”), a biological interaction that is not part of the complement pathway at all. (EX1004 ¶ [0192].) Samsung does not and cannot explain why a POSA seeking a safe and effective anti-C5 antibody composition for the treatment of PNH would have looked to Bowdish. *See, e.g., Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013).

Likewise, Mueller PCT, and the associated Mueller 1997, concerned an issue unrelated to the '504 patent—developing antibodies to VCAM molecules to block transplant rejection. (EX1009 at 8:23-26, 37:22-36; EX1006 at 441-444.) As with Bowdish, a POSA would not have looked to Mueller for guidance on designing antibodies for blocking C5 cleavage or treating PNH. Rather, Mueller described anti-VCAM 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 VCAM. (EX1009 at 12:19-32; EX1006 at 442-443.)

Samsung also cannot explain why a POSA would have turned to Bowdish or Mueller for a description of “eculizumab.” Critically, neither Bowdish nor Mueller mention the term “eculizumab.” 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 and would have instead looked to the Bowdish and Mueller references addressing unrelated problems.

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 at 10-12.) As Samsung acknowledges, 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 at 9 (citing EX1010 at 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 at 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 at 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 the IgG4 antibody of Thomas. (See, *e.g.*, Petition at 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 C<sub>H</sub> region. (ALXN2022, ¶¶ 203, 208.)

Likewise, Mueller’s reference to “h5G1.1 CO12 HuG2/G4 mAb” for use as an experimental isotype control (EX1009 at 9:6-9, 12:34-37) would not have taught a POSA about the structure of the “eculizumab” described in the literature as being safe and effective for the treatment of PNH. For example, Mueller also uses an “h5G1.1” antibody with an IgG4 heavy chain (“h5G1.1 CO12 HuG4 mAb”) as an isotype control (see EX1009 at 11:36-12:4, Figures 11-13; *see also* EX1006 at 444-445, Figure 3) and 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. To the contrary, the literature as of March 15, 2007 clearly taught a POSA that the

“eculizumab” antibody used in the Phase II and Phase III PNH studies was Thomas’s IgG4 isotype. (See Table 1.)

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 Thomas’s antibody structure 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, 2017 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, IV.B.) Thomas predicted that its IgG4 antibody would be potent in preventing C5 cleavage and “minimally immunogenic in patients” (EX1010 at 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 Section II.C, IV.B.)

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 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 at 506, 508; ALXN2017 at 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 at 2240, 2242 (showing that antibodies expressing the same variable regions but different C<sub>H</sub> regions “bind [antigen] with **significant differences in affinity**”); ALXN2008 at 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 at 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 at 3 (review 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<sub>H</sub>1” 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 at 3388, 3391-92; ALXN2009 at 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 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 at 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 antibody—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<sup>®</sup> (*see, e.g.*, EX1044 at 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<sup>®</sup>—first approved *after* March 15, 2007—was the *first* FDA approved antibody with its uniquely-engineered C<sub>H</sub> region.

**C. Samsung Fails to Show that All Elements of the Claimed Pharmaceutical Compositions of the '504 Patent Were Disclosed in the Prior Art**

Samsung also cannot show any teaching in the prior art of the additional elements of the '504 patent claims. For example, neither Bell nor Wang discloses the elements of a “300 mg single-use dosage form” or “30 ml of a 10 mg/ml antibody solution.” Bell merely described administration of 600 and 900 mg doses

of “eculizumab” without identifying the dosage unit or concentration. (EX1007 ¶¶ [0082], [0091]; ALXN2024, ¶¶ 69-80.<sup>11</sup>) And Wang described a broad range of possible concentrations (1-200 mg/ml) for formulating various antibodies (EX1044 ¶ [0067]), without teaching the specific 10 mg/ml antibody concentration of the ’504 patent’s claimed antibody. (ALXN2024, ¶¶ 81-90.) Samsung cannot explain how a POSA without hindsight would have arrived at the specific dosage unit, concentration and volume recited in the claims of the ’504 patent with any reasonable expectation of success.

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<sup>11</sup> The Declaration of Dr. Bernhardt Trout (ALXN2024), a renowned expert in the field of antibody formulation and stabilization, was submitted in IPR2019-00739 in support of Patent Owner 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. Ippoliti. Therefore, Alexion cites to it for support in this Patent Owner Preliminary Response. Alexion reserves the right to submit one or more expert declarations specifically directed to Samsung’s petition if any Grounds are instituted.

V. **A PERSON OF ORDINARY SKILL IN THE ART**

Alexion does not dispute Samsung's POSA definition (Petition at 15-16), 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*. Under either description of a POSA, Samsung cannot prove unpatentability of the challenged claims of the '504 patent under any of its fatally flawed Grounds.

VI. **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 ignores the clinical art's teachings that eculizumab had Thomas's IgG4 heavy chain and, instead, uses hindsight to combine four other disparate references. It incorrectly contends that a POSA reading Bell—which does *not* disclose eculizumab's sequence, but rather cites to Thomas—would somehow be motivated to combine Bowdish and Evans to reach eculizumab's sequence. Bowdish does not provide *any* disclosure of an antibody having SEQ ID NOs: 2 and 4. Nor does Bowdish disclose “eculizumab” or any other C5-binding antibody. Even Samsung admits that Bowdish fails to disclose the claimed heavy chain CDR3. (Petition at 20.)

To make the combination, Samsung must ignore Bowdish's incorporation-by-reference of Evans' 5G1.1 **murine** framework region and its **lack** of incorporation of any other sequences. Samsung must also ignore that Evans did not describe **any** full-length humanized C5-binding antibodies, let alone the claimed antibody.

Ground 1 also fails for proof because Samsung admittedly neglected to rely upon the actual document that Bowdish cites, the '283 application, which is not the Evans patent. But, even using Evans as a stand-in for the '283 application (which it is not), Samsung overreads Bowdish's single reference to Evans for "[c]onstruction of 5G1.1," a **mouse** antibody that is nowhere close to the claimed **humanized** antibody. Samsung cannot rewrite Bowdish's limited reference to construction of Evans' "5G1.1" mouse antibody as an open-ended incorporation of Evans' entire 93-page disclosure, including sequences that are **not** the "5G1.1" antibody.

Even if Bowdish and Evans were combined, a POSA without hindsight would not have arrived at the claimed sequence. Rather, a POSA would have seen Bowdish and Evans as pointing in different directions, with Bowdish referring to a **mouse** antibody in its reference to "[c]onstruction of 5G1.1" from the '283 application; and Evans disclosing only a mouse antibody plus humanized

recombinant “fragments” that are unusable as the “scaffold” to make Bowdish’s full-length TPO-mimetic compound.

Finally, both Mueller PCT and Tacken are directed to completely different antibodies and contain, at best, peripheral and ambiguous clues about eculizumab’s constant region, which cannot contradict the clinical art’s clear teaching that “eculizumab” had Thomas’s IgG4 heavy chain.

In Ground 1 (and Ground 3), Samsung impermissibly culls and combines bits of multiple and unrelated references in hindsight to reconstruct the claimed sequences. Such hindsight-driven analysis—starting with the claimed sequence and working backwards to reconstruct it—is always improper. *See, e.g., Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (warning against “slipping into use of hindsight” and “the temptation to read into the prior art the teachings of the invention in issue”); *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2017) (warning against “the distortion caused by hindsight bias” and “arguments reliant upon *ex post* reasoning”).

Finally, Samsung simply glosses over and dismisses the formulation and administration limitations of the claims, and fails to show how they are disclosed in Bell or any other reference.

Samsung admits that Bowdish alone does not disclose SEQ ID NOs: 2 and 4, but instead relies on a limited “incorporation by reference of Evans” (Petition at 30) that does **not** include anything other than construction of the 5G1.1 **murine** sequence: “The TPO mimetic peptide graft in Fab clone X4b has been transplanted into the heavy chain CDR3 region of another antibody framework, 5G1.1 . . . . Construction of 5G1.1 is described in U.S. Application Ser. No. 08/487,283 incorporated herein by reference.” (EX1006, ¶ 191.<sup>12</sup>) Notably, Bowdish does not incorporate any of Evans’ scFv sequences, including the

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<sup>12</sup> In IPR2019-00739, Alexion submitted the Declaration of Dr. Michel Nussenzweig (ALXN2026) regarding the sequence of the genetic material of the hybridoma maintained by ATCC, corresponding to Evans’ murine antibody sequences, to determine the sequence of the “5G1.1” mouse antibody incorporated by reference into Bowdish. As Dr. Casadavell explained, a POSA comparing that “5G1.1” sequence to Bowdish’s Figs. 13A and 13B sequences would see misalignment beyond the region of Bowdish’s TPO-mimetic peptide, and would not have further envisioned any combination of sequences that would result in the claimed antibody. (ALXN2022, ¶¶ 211-216.)

HCDR3 sequence admittedly missing from Bowdish. (See ALXN2022, ¶¶ 209-219.)

Contrary to Samsung's suggestion (Petition at 31), Bowdish does not "explain[] that it created SEQ ID NO:67 from a starting heavy chain sequence that is identical to SEQ ID NO:2." It makes no reference to eculizumab, and instead references Evans' murine 5G1.1 heavy chain sequence. (EX1004, ¶ 191.) Nor does Bowdish identify the "native CDR3" of Evans' antibody as eculizumab. (Petition at 32.) Thus, Samsung's obviousness story and after-the-fact sequence comparisons (Petition at 31) are just hindsight obviousness arguments using the claims as a roadmap.

Nor can Samsung show, without hindsight, how a POSA would have been motivated to select and combine Bowdish and Evans, in view of Bell, Tacke, and Mueller PCT, or how they could have reasonably expected to succeed in doing so. The Supreme Court and the Federal Circuit have repeatedly warned against this type of hindsight bias. *See, e.g., Graham*, 383 U.S. at 36; *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”). Samsung uses its present-day knowledge of the ’504 patent to reconstruct its unique antibody sequence from bits of art, including the non-analogous Bowdish reference that a POSA would not have considered without hindsight, and simultaneously ignores the art’s consistent teaching towards Thomas’s IgG4 heavy chain as “eculizumab”—which ***taught away*** from the claimed invention. Accordingly, Samsung’s Ground 1 fails.

Samsung cannot explain why a POSA seeking to develop an anti-C5 antibody composition for treating PNH would have started with Bowdish, which has 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 non-analogous art to the ’504 patent. *See, e.g., Circuit Check 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 their TPO activity was unrelated to the complement pathway or C5. Without hindsight, a POSA would not have “look[ed] to [Bowdish] to solve the particular problem” solved by the ’504 patent. *Circuit Check*, 795 F.3d at 1335.

Further, Samsung's hindsight-driven contention that a POSA would have reverse-engineered "eculizumab" by substituting Evans' heavy chain CDR3 sequence into Bowdish's TPO-mimetic construct lacks support. *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 contrary assertions further confirm its reliance on hindsight. (*See, e.g.,* Section IV.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 myriad of possible murine and humanized antibodies and fragments not limited to "eculizumab." (*See* Section IV.A.2.b.) Evans, in turn, described only variable region fragments of anti-C5 antibodies, not the constant region of "eculizumab" or any other complete humanized anti-C5 antibody. (*See* Section IV.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 them all. (Petition at 52.) A POSA without hindsight would have had **no reason** to believe that combining Bowdish's TPO-mimetic construct with one of Evans' many sequences would lead to "eculizumab." (*See* ALXN2022, ¶¶ 208-223.)

Samsung exacerbates its hindsight error by ignoring the art's (including Bell's) **actual** teaching as of 2007 of the structure and sequence of "eculizumab" as being Thomas's IgG4 antibody. (See Table 1.) Samsung cannot explain why a POSA, without hindsight, would have ignored these clear teachings and instead turned to non-analogous art (*i.e.*, Bowdish) to experiment with different antibody sequences that were **not** known to have anti-C5 activity or studied in humans. Rather, the art's teachings towards Thomas would have left the POSA with no motivation to try such unwarranted, unpredictable experimentation with Bowdish's TPO-mimetic constructs (*see* ALXN2022, ¶¶ 225-234). *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d356, 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 in a composition for preventing C5 cleavage 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). Instead, a POSA would have understood that even small changes to the amino acid sequence could have a substantial impact on the binding properties, safety, and efficacy of an antibody, and would not have reasonably foresaw a cobbled-together, hindsight-driven antibody using Bowdish and Evans, which differed from Thomas's IgG4

antibody. (See Section IV.A.) A POSA had no reason to undertake extensive testing of such an antibody when the art already taught that Thomas’s “eculizumab” was thoroughly studied and shown to be a clinical success. (See ALXN2022, ¶ 233, Figure 14.) Notably, both Bell and Tacken, if consulted, would have also led the POSA to Thomas.

Mueller, as an anti-VCAM reference, would not have been consulted. If it were, however, it also teaches away. As the Board noted in IPR2019-00740, Mueller identified **only** an **IgG4** isotype antibody (*i.e.*, Thomas’s isotype) 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 at 57.)

Samsung’s proposed sequence comparisons (Petition at 30-33) and “routine alignments” (Petition at 38-39) are, again, the epitome of hindsight. A POSA would have had to work backwards from the claimed sequence to make sense of these comparisons and alignments and would never have been motivated to make them given the disparate nature of the references: Bowdish (TPO-mimetic peptides), Mueller (anti-VCAM 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 at 39) except with the benefit

of hindsight and by ignoring the reference to Evans' 5G1.1 murine antibody.  
(Petition at 40 (admitting that Evans discloses "the original mouse antibody 5G1.1").)

Samsung also cannot show how the "300 mg single unit dosage form" element of claim 5 would have been obvious to a POSA without hindsight. Samsung presumably relies on Bell for this element. But Bell described administration of 600 and 900 mg doses of "eculizumab" without identifying the dosage unit or concentration of the administered composition. (EX1007, ¶¶ [82], [91]; ALXN2024, ¶¶ 69-80).) Samsung does not explain how a POSA without hindsight would arrive at claim 5's specific dosage unit form with any reasonable expectation of success.

Accordingly, Ground 1 fails the standard for institution because Samsung cannot show obviousness with Bell, Bowdish, and Evans, in view of Tacke, and Mueller PCT.

**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**

Ground 2 adds Wang (EX1044) to an already unwieldy combination, and attempts to argue that the art collectively renders obvious the use of eculizumab's novel sequence in the claimed 300 mg formulation and 10 mg/ml solution. Ground

2 fails for the same reasons as Ground 1 and because neither Wang nor Bell makes such disclosures.

Samsung cannot show how the other elements of claim 6 would have been obvious to a POSA without hindsight. Regarding Bell and Wang, Samsung implicitly concedes that neither discloses them. (Petition at 49-50.) Bell merely described administration of 600 and 900 mg doses of “eculizumab” without identifying the dosage unit or concentration of the administered composition. (EX1007, ¶¶ [82], [91]; ALXN2024, ¶¶ 69-80.) Wang described a broad range of possible concentrations (1-200 mg/ml and 40-200 mg/ml) for various antibodies (EX1044, ¶ [67], Fig. 10), without teaching the claimed 10 mg/ml concentration (ALXN2024, ¶¶ 81-90). Nor does Samsung explain how a POSA without hindsight would arrive at the elements of claim 6 with any reasonable expectation of success.

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

Ground 3 fares no better. As with Ground 1, Samsung ignores the clinical art’s teachings that eculizumab had Thomas’s IgG4 heavy chain and, instead, uses hindsight to combine three other disparate references. It incorrectly contends that a

POSA reading Bell—which cites to Thomas—would be motivated to combine Evans and Mueller PCT to reach eculizumab’s sequence.

Samsung attempts to combine Evans and Mueller PCT “in view of Tacken.” But, again, Evans discloses only the 5G1.1 **murine** antibody and Mueller relates to a different anti-VCAM antibody. As the Board noted in IPR2019-00739 (with Tacken before it), “[i]t is not apparent that the skilled artisan, knowing of Evans, would have looked to Mueller, or vice versa.” (Paper 15 at 54.) Mueller identified **only** an **IgG4** isotype antibody “h5G1.1 CO12 HuG4 mAb” (*i.e.*, Thomas’s isotype) as “directed against human C5” and taught nothing about the C5 binding or properties of “h5G1.1 CO12 HuG2/G4 mAb.” (*Id.*)

Nor would a POSA have been motivated to combine the sequences in Evans and Mueller PCT, neither of which cites to each other, in the exact manner to get the claimed sequence. As the Board previously recognized, nothing in Evans or Mueller PCT instructs whether or how such a combination should be done, including “the proposed reasons one of ordinary skill in the art would have paired Evans with Mueller, choosing precisely those portions of Evans’s and Mueller’s constructs to create an antibody having exactly the sequences set forth [in] SEQ ID Nos: 2 and 4.” (IPR2019-00739 (Paper No. 15 at 54).)

Even if a POSA were motivated to combine Evans and Mueller PCT, viewing them in light of Bell and Tacken would have led the POSA further astray, as both of those references cited to Thomas's IgG4 sequence.

Samsung also fails to show how the formulation or administration limitations of claims 1-5 and 7-10 are disclosed in any of its references.

Mueller did not include any data on C5 binding, blocking C5 cleavage, or treating PNH. Mueller exclusively describes “h5G1.1” antibodies, with either IgG4 or “IgG2/G4” heavy chains, as “isotype control” antibodies for studying anti-VCAM activity. (EX1009 at 9:6-9, 12:19-37; EX1006 at 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” as long as it did not bind to VCAM.

Nor can Samsung show that a POSA, without hindsight, would have reasonably expected success with an antibody formed from combining a variable region from Evans with the “IgG2/G4” C<sub>H</sub> region of Mueller's anti-VCAM antibodies and “negative controls.” A POSA in early 2007 would have understood that “eculizumab”—the antibody shown to prevent C5 cleavage and safely and effectively treat PNH—was Thomas's **IgG4** antibody. (See Section IV.A.1.) A POSA would not have deviated from this teaching of “eculizumab” to instead make a different antibody that a POSA would not have reasonably expected to still

block C5 cleavage or to safely and effectively treat PNH. (See ALXN2022, ¶¶ 238-262.) In fact, a POSA at that time would not have known of **any** human clinical testing reporting the safety of antibodies using the “IgG2/G4” hybrid.

Samsung again uses hindsight to pick and choose specific sequences to combine for sequence alignments and comparisons. (Petition at 53-55). But nothing in Evans or Mueller teaches that such a combination should be done, what it should be compared to, or whether it would result in an effective anti-C5 antibody. Again, as the Board previously recognized, Samsung’s argument is pure hindsight. (See also, ALXN2022, ¶¶ 238-262.)

**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 disclose 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, which discloses an anti-VCAM antibody, with Evans, which discloses

only the 5G1.1 mouse antibody and multiple scFv's. The Board already rejected this argument. (*See* Section VI.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 VI.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 reverts back to Bell only and argues inherency. But Bell does not disclose any antibody sequence and describes "eculizumab" as ***Thomas's IgG4 antibody***. Samsung again disregards Bell's (and the whole art's) clear teaching towards Thomas, and ignores the established record regarding the confidentiality of the clinical trials, including Bell's.

Worse, Samsung misstates that "[n]o prior art reference anywhere states that 'eculizumab' has an IgG4 isotope" and that "the only disclosure in the prior art as to the constant domain structure of 'eculizumab' is Tacken, which unambiguously states that it has the IgG2/IgG4 structure." (Petition at 60.) Conversely, practically every prior art reference mentioning eculizumab, including Bell and Tacken, referenced Thomas's IgG4 isotype.

Here, Samsung recycles its hindsight obviousness arguments as "enablement" and "inherent" anticipation. (Petition at 61-62.) But neither this 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 at 59) changes the facts that the sequences were **unknown** as of Bell’s publication and that the art lead to Thomas.

As Samsung admits, Bell does not expressly or inherently disclose all the elements recited in claims 1-5 and 7-10. *See, e.g., Therasense, Inc. v. Becton Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) (“Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim.”); Petition at 29 (“Bell’s disclosure does not include the exact amino acid sequence of eculizumab). Significantly, **nothing** in Bell taught the uniquely-engineered heavy chain reflected in “SEQ ID NO: 2.” (See Section VI.A.) Rather, Bell referenced Thomas’s **IgG4** antibody. Specifically, Bell cited Thomas as describing “[m]ethods for the preparation of h5G1.1-mAb . . . under the tradename eculizumab”<sup>13</sup> (EX1007, ¶ [0052]), and described positive Phase II

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<sup>13</sup> While Bell’s paragraph [0052] 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 incomplete antibody sequences without a C<sub>H</sub>

clinical results for “eculizumab” in PNH patients (EX1007, ¶¶ [0081]-[0095]).

Bell thus would have taught away from other antibody constructs that lacked such published reports of clinical safety and efficacy.

Nor could Bell have enabled a POSA to make and use the claimed antibody without undue experimentation because Bell (and the whole art) guided a POSA to make and use a different antibody—Thomas’s **IgG4** antibody (ALXN2022, ¶¶ 195-199). *See, e.g., Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Rsch.*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) (regarding anticipation, “[i]t is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation”).

Samsung implicitly concedes that Bell did not disclose or enable the claimed invention because Samsung’s theory of “enablement” requires a POSA to combine bits of the claimed sequence from other prior art documents, including, *e.g.*, Evans, Bowdish, Mueller, and Tacken. (Petition at 61-62.) These arguments are thus Samsung’s recycled obviousness arguments from Grounds 1-4 shoehorned into an alleged inherent 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

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region. (*See, e.g.*, EX1005 at 43:6-14, 43:62-45:4.)

limitation of a claim must be found in a single reference . . . [and] does not permit an additional reference to supply a missing claim limitation.”). Samsung has also failed to show that a POSA provided with Bell, Evans, Bowdish, Mueller, or Tacken references as of March 15, 2007 would have been led to the claimed 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 IV.A.1.)

Acknowledging Bell’s failure to expressly disclose the claimed sequence, Samsung is forced to turn to non-prior art, post-filing information regarding the sequence of SOLIRIS® to make an “inherent anticipation” that misapplies the law and misstates the facts. (See, *e.g.*, Petition at 58-61.) Specifically, Samsung alleges inherent anticipation on the grounds that **today**—years after the ’504 patent’s priority date—it is known that Bell’s clinical study **actually** used an antibody with SEQ ID NOs: 2 and 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 that product’s specific structure or composition if a POSA could not have **necessarily** determined the later claimed structure/composition from public information available as of the priority date. See, *e.g.*, *Endo Pharms. 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 used in the studies underlying prior art clinical publications is insufficient to give rise to inherent anticipation. *See, e.g., id.; Bayer CropScience LP v. Syngenta Ltd.*, IPR2017-01332, Paper 15 at 3-6 (Apr. 2, 2018).

Accordingly, Samsung has not shown inherent anticipation of the claims 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. Conversely, as discussed above, a POSA reading Bell would have envisioned Thomas’s “eculizumab” antibody. (See Section IV.A.1.) And the use of the “eculizumab” name alone does not constitute disclosure of the actual antibody sequence, particularly when a POSA as of March 15, 2007 would have understood that name to refer to a different sequence. *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 clinically-tested antibody sequence. Rather, as discussed in the Boone Declaration during prosecution (EX1002 at 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.F.) 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. Moreover, a POSA attempting to determine the sequence of “eculizumab” as described in Bell would have followed that publication’s reference to Thomas. (See Section IV.A.1.)

Alexion’s so-called admissions are neither relevant nor binding. (Petition at 59-60.) Samsung’s *Southwall Techs.*, *Gillette*, and *Apple* cases (Petition at 60) relate to using statements made during prosecution as intrinsic evidence during claim construction. For inherent anticipation, what matters is what the art actually taught as of the priority date. Here, before March 15, 2007, the art consistently taught that “eculizumab” was Thomas’s IgG4 isotype, **not** the claimed sequence. Bell did not teach anything different.

Ground 5 thus fails the standard for institution because Samsung fails to show the presence in Bell of all of the claimed elements.

**F. The Objective Indicia of Nonobviousness Support Validity**

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).

SOLIRIS<sup>®</sup>, the commercial embodiment of the '504 patent, is a 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<sup>®</sup> 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 [2018 10K] at 70.) The outstanding economic performance of SOLIRIS<sup>®</sup> has a direct nexus to the patented features of the '504 patent, which claims methods of treating PNH comprising administering pharmaceutical compositions of 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<sup>®</sup> 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<sup>®</sup> “orphan drug” status for PNH. (ALXN2019 [Ricklin] at 1270.) *See, e.g., Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994, 997-998 (Fed. Cir. 2009). SOLIRIS<sup>®</sup> 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 says that its intent to develop a biosimilar copy of SOLIRIS<sup>®</sup> 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 at 65.) 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](https://clinicaltrials.gov).) Instead, they chose to copy SOLIRIS<sup>®</sup>.

Samsung's denial of the existence of secondary considerations of non-obviousness is just a rehashing of its prior art obviousness arguments. (Petition at 63-65.) In short, Samsung argues 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 a nexus between those sequences and those indicia. As distinguished from *Ormco Corp v. Align Tech., Inc.*, 463 F.3d 1299,

1312 (Fed. Cir. 2006), the unique claimed sequences are “the feature that creates the commercial success” and other indicia of non-obviousness here. Contrary to the arguments in Samsung’s Grounds, those sequences were novel and non-obvious at the time of the invention.

**VII. CONCLUSION**

For the reasons described herein, Alexion respectfully submits that the Board should deny Samsung’s petition for *inter partes* review.

Respectfully submitted,

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**CERTIFICATION OF SERVICE**

The undersigned hereby certifies that the foregoing **PATENT OWNER'S PRELIMINARY RESPONSE** and **EXHIBITS ALXN2005-2026 and ALXN2098-2102** were served via electronic mail on September 12, 2023, in their entirety on the following:

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**CERTIFICATION OF WORD COUNT**

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