UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2023-00933
Patent: 9,732,149

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

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EXHIBIT LIST[1]

Exhibit No.	Description of Document
2000 to 2004	*Intentionally left blank*
2005	SOLIRIS® Label
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2007	Janeway and Travers, *Immunobiology:* The Immune System in Health and Disease (Garland Science, 6thed. (2005))
2008	McCloskey *et al.*, Human Constant Regions Influence the Antibody Binding Characteristics of Mouse-Human Chimeric IgG Subclasses, IMMUNOLOGY, 88: 169-173 (1996)
2009	Torres *et al.*, The Immunoglobulin Heavy Chain Constant Region Affects Kinetic and Thermodynamic Parameters of Antibody Variable Region Interactions with Antigen, J. OF BIOL. CHEM., 282(18): 13917–27 (2007)
2010	Janda *et al.*, Ig Constant Region Effects on Variable Region Structure and Function, FRONT. MICROBIOL., 7(22): 1-10 (2016)
2011	Pritsch *et al.*, Can Immunoglobulin CH1 Constant Region Domain Modulate Antigen Binding Affinity of Antibodies?, J. CLIN. INVEST., 98(10): 2235-43 (1996)

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

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2016	U.S. Patent No. 7,482,435, issued to Bowdish *et al.*
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2021	BusinessWire, Alexion's Soliris® Receives 2009 Prix Galien France for Most Innovative Drug for Rare Disease, June 10, 2009, available at https://www.businesswire.com/news/home/20090610005826/en/Alexions-Soliris®-Receives-2009-Prix-Galien-France (last visited May 15, 2019)

2022	Declaration of Arturo Casadevall, M.D., Ph.D.
2023 to 2025	*Intentionally left blank/Reserved*
2026	Declaration of Michel C. Nussenzweig, M.D., Ph.D.
2027 to 2097	*Intentionally left blank/Reserved*
2098	Harlow and Lane, Chapter 2:Antibody Molecules, in *Antibodies, A Laboratory Manual* (1988)
2099	*Intentionally left blank*
2100	Rother, R., *et al.*, "Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria," *Nature Biotechnology* 25: 1256-1264 (2007)
2101	Prosecution History for U.S. Patent No. 9,718,880 B2, submitted by Petitioner Samsung BioEpis Co., Ltd. in IPR2023-00998 as EX1002
2102	Prosecution History for U.S. Patent No. 10,590,189 B2, submitted by Petitioner Samsung BioEpis Co., Ltd. in IPR2023-01069 as EX1002
2103	Prosecution History for U.S. Patent No. 9,725,504 B2, submitted by Petitioner Samsung BioEpis Co., Ltd. in IPR2023-00999 as EX1002

I. INTRODUCTION

Alexion provides the following Preliminary Response to Samsung's Petition seeking review of claim 1 of Alexion's U.S. Patent No. 9,732,149 ("the '149 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 '149 patent, in prior IPRs brought by Amgen, and during prosecution of similar claims subsequently granted by the Examiners in child patents to the '149 patent. Further, each of Samsung's Grounds is fatally flawed by hindsight and fails to prove that the challenged claim is 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,[2] 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. Patent Nos. 10,590,189 ("the '189 patent") and 10,703,809 ("the '809 patent"),

[2] IPR2019-00739 (U.S. Patent No. 9,725,504 ("the '504 patent"); IPR2019-00740 (U.S. Patent No. 9,718,880 ("the '880 patent"); IPR2019-00741 (the '149 patent).

child patents to the '149 patent. Despite working on its proposed biosimilar of SOLIRIS® since as early as 2018,[3] beginning comparative trials in the U.S. in 2019,[4] 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 four 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 claim 1 of the '149 patent and commercialized as Alexion's groundbreaking orphan disease therapy known today as SOLIRIS®. Before March 15, 2007, the priority date of the '149 patent, however, the unique amino acid sequence of SOLIRIS® was not publicly known or disclosed in the prior art. Samsung's

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

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

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 IPR2019-00741 (*see, e.g.*, ALXN2022, ¶¶ 138-171, 182-252),[5] the arguments in Samsung's Petition amount to little more than a post-hoc narrative

[5] The Declaration of Dr. Arturo Casadevall, a renowned expert in the field of immunology and antibodies, was submitted in IPR2019-00741 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.

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 claim 1 is 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

Claim 1 of the '149 patent covers the 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 lead to downstream effects of the complement pathway, including hemolysis in PNH patients. When SOLIRIS® is administered, however, it binds to a critical location ("epitope") on C5 with sufficient affinity and specificity to prevent cleavage of C5, thus blocking

the effects of the complement pathway and sparing PNH patients' red blood cells from destruction. (*See* ALXN2100 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_L") and a portion of the heavy chains ("V_H"). (ALXN2007 at 105-06.) Likewise, the constant region is comprised of a portion of the light chains ("C_L") and a portion of the heavy chains ("C_H"). (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.

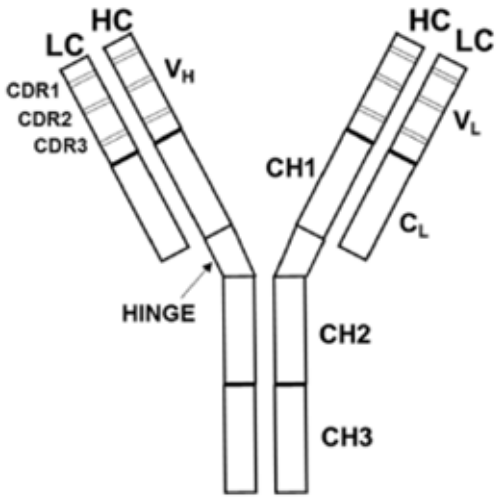


Figure 1: Basic structure of an IgG antibody

(*See* ALXN2022, ¶¶ 62-68.)

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 heavy chain constant 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; *see also* 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, ¶ 80.)

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

A POSA as of March 15, 2007 would have understood that Alexion had developed a humanized antibody named "eculizumab," which bound to human C5 and blocked its cleavage, and was shown in Phase II and Phase III human clinical trials to be safe and effective for the treatment of PNH. (EX1011 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 '149 patent, including the uniquely-engineered C_H region reflected in "SEQ ID NO: 2." Rather, the literature taught a POSA that "eculizumab" contained an "***IgG4***" C_H region that is ***very different*** from "SEQ ID NO: 2" of the '149 patent.

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_H region, which was selected because the IgG4 isotype was thought to avoid activating human complement. (EX1010 at 1396, 1399.[6]) 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; *see also* ALXN2022, ¶¶ 122-123.)

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

Today, but ***not*** before the March 15, 2007 priority date for the '149 patent, it is known that SOLIRIS® has the amino acid sequence recited in the '149 patent's claim 1, namely, "a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." A POSA before the '149 patent, however, would

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

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.

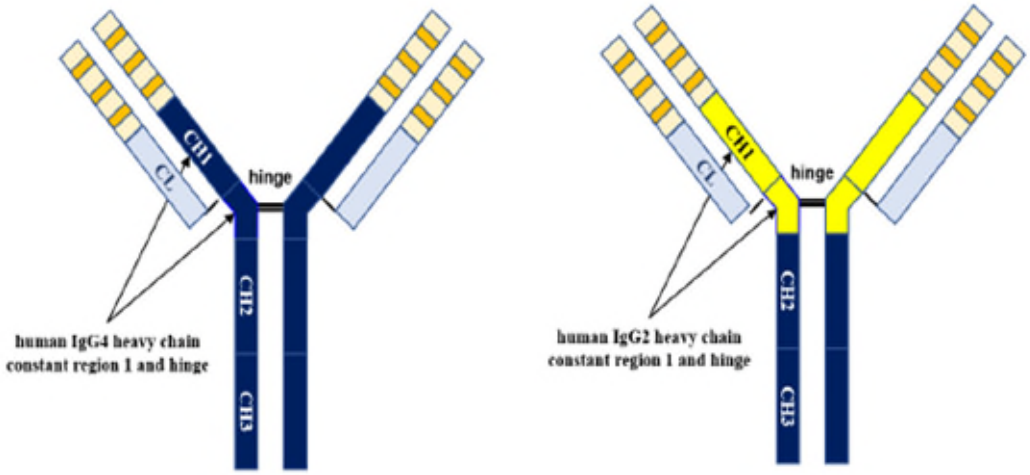
Today, but ***not*** before March 15, 2007, it is known that SOLIRIS® is a unique antibody that is ***very different*** from the humanized IgG4 antibody described in Thomas. As understood today, but not as of March 15, 2007, the heavy chain of SOLIRIS® (SEQ ID NO: 2) features a non-naturally occurring, uniquely-engineered constant region—containing sequences from both human IgG2 and IgG4—designed by scientists at Alexion and thoroughly tested in clinical trials. (ALXN2100 at 1257-1258.) Notably, SOLIRIS® was the first FDA-approved product containing Alexion's uniquely-engineered C_H region. A POSA as of March 15, 2007 would not have been aware of any published clinical testing showing that an antibody with this uniquely-engineered constant region would be safe or effective for human therapeutic use.

The structure of eculizumab that is known today and claimed in the '149 patent is shown below compared to the IgG4 isotype antibody described in Thomas, which the literature before March 15, 2007 would have taught a POSA was "eculizumab." Unlike Thomas's IgG4 antibody, the claimed antibody uses the

C_H1 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®, having a non-naturally occurring, protein-engineered isotype



(*See* ALXN2022, ¶¶ 134-136.)

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 above 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 ¶¶ 141-147.) 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 at 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

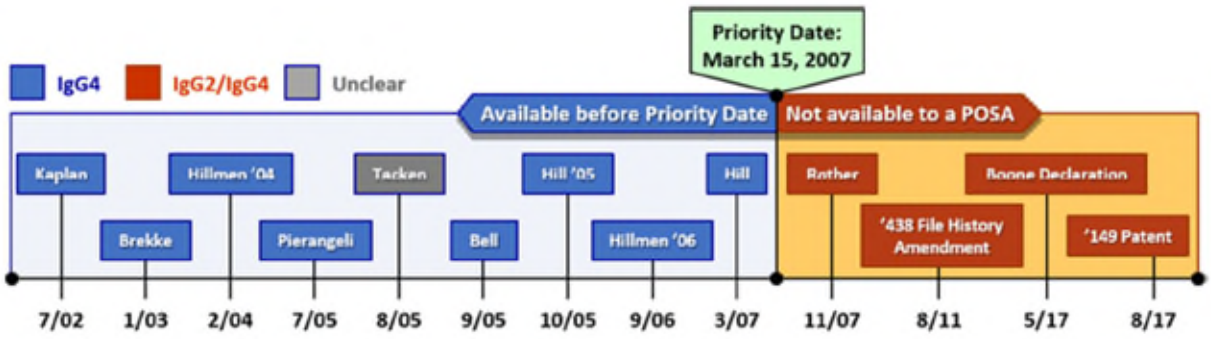
> constant region, is specific for the human terminal complement protein C5.***(19)***

(EX1008 at 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 ¶¶ 141-150.) 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 ¶¶ 146, 150). *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. ’149 Patent Overview

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

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

(EX1001 at 39:1-4.)

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

In the course of the ’149 patent’s prosecution, as well as prosecution of the related ’504 patent,’880 patent,’189 patent, and ’809 patent, the Examiner

considered the same, or substantially the same, prior art and arguments that Samsung now asserts in its Petition. In doing so, the Examiner made findings undermining Samsung's positions in its Petition, including that (1) none of the art recited an antibody with a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4, and (2) a POSA "would not have been easily guided to mak[e] antibodies with these recited sequences." (EX1002 at 1314.) The Examiner also found that SOLIRIS® and its unique sequence was not "accessible to the public" as of March 15, 2007. (*Id.*)

For example, in finding claim 1 of the '149 patent to be novel and nonobvious, the Examiner:

- Expressly discussed Samsung's asserted reference Evans (EX1005), as well as Hillmen 2004 (EX1011) (which is cumulative in all material respects here to Samsung's asserted reference Bell (EX1007)), before finding claim 1 allowable (*see*, *e.g.*, EX1002 at 842-843, 1079-1081);
- Considered Samsung's asserted reference Bell (EX1007), which Alexion submitted to the PTO (*see*, *e.g.*, EX1002 at 847, 854, 861);
- 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 846); and

- Considered the Mueller 1997 article (EX1006), which is cumulative of Samsung's asserted Mueller PCT reference (EX1009) because it discloses the same antibodies as Mueller (*see, e.g.*, EX1002 at 863).

Notably, during prosecution of the '149 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." (ALXN2103 at 1038, 1118 (citing EX1011); *see also* EX1002 at 1079 (Examiner stating that "Hillmen . . . teaches that 'eculizumab' is a recombinant humanized antibody that binds to C5 . . . and cites ***Thomas***").) Alexion also submitted a declaration of co-inventor Dr. Leonard Bell during prosecution of the related '504 patent, explaining how a POSA reading Hillmen's reference to Thomas would have been guided toward an antibody with a "naturally-occurring IgG4 heavy chain," and would not have envisioned the very different antibody of the '149 patent. (ALXN2103 at 1079-1080, 1084 ¶¶ 3-5.) Ultimately, the Examiner agreed that the prior art did not disclose or suggest the

specific antibody sequence in the '149 patent's claim 1. (EX1002 at 1314; *see also* ALXN2103 at 1347.)

Samsung also ignores the Declaration of Dr. Laural Boone (EX1002 at 1276-1283 ("the Boone Declaration")), which the Examiner credited as showing that Alexion's clinical studies of the claimed antibody did not disclose its sequence or render it publicly accessible. (EX1002 at 1314-1315.) 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 1280-1283 ¶¶ 6-13, 1314-1315.) While, as Dr. Boone explained, it is known ***today*** that SOLIRIS® as used in these studies had the claimed sequence (EX1002 at 1280 ¶ 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 '149 patent. (EX1002 at 1314-1315.)

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):

References Considered in Prosecution Histories (PH)				
	'149 PH	Amgen IPRs†	'809 PH	'189 PH
Bowdish	'435 patent[7]	✓	✓	✓
Evans	✓	✓	✓	✓
Mueller PCT/1997	Mueller 1997[8]	✓	✓	✓
Tacken		✓	✓	✓
Bell/Hillman/Hill	✓	✓	✓	✓
Wang	✓	✓	✓	✓
† All cited in the prosecution histories of the '809 and '189 patents				

[7] The '435 patent is cumulative to Bowdish.

[8] Mueller 1997 is cumulative of Mueller PCT.

Arguments Considered in Prosecution Histories (PH)				
	’149 PH	Amgen IPRs	’809 PH	’189 PH
Bowdish & Evans		✓	✓	✓
Mueller & Evans		✓	✓	✓
Bell/Hillman/Hill	✓	✓	✓	✓
Bell & Wang	✓	✓	✓	✓

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 the Examiners 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 sequences. Samsung has not shown error in the Examiner’s evaluation of the art and 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 (EX1009)[9]), Thomas, Hillmen,

[9] Mueller PCT and Mueller 1997 each discuss antibodies directed against porcine VCAM protein and their use in methods related to human rejection

Hill, and 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 (EX1004) and Bell (EX1007) were cited in IDS's during the prosecution of the '880, '504, and '149

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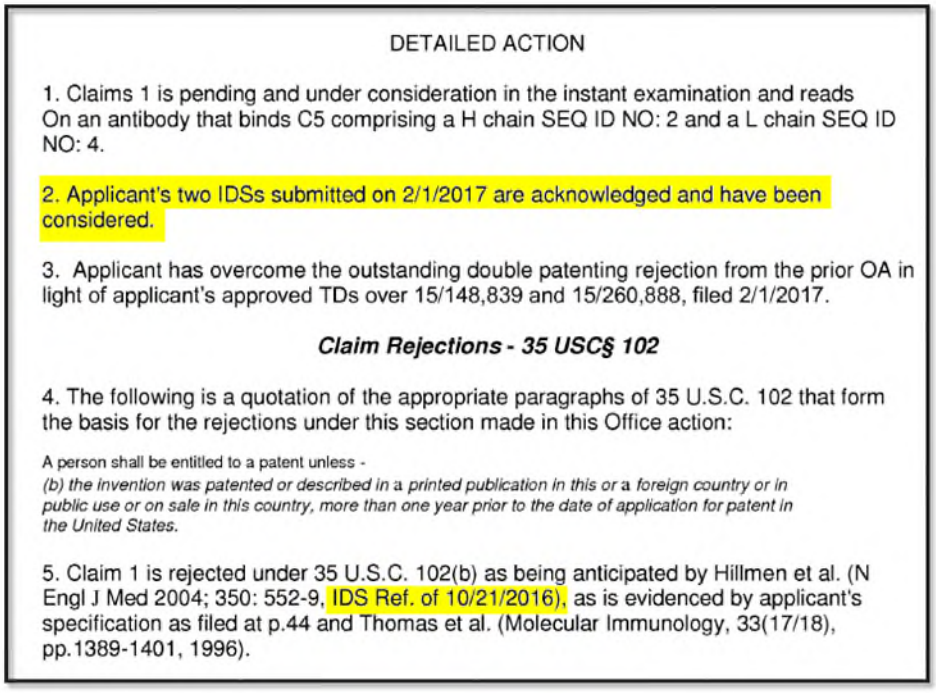
of porcine xenotransplants. (EX1006, Abstract; EX1009, Abstract.) Both discuss the same two VCAM-blocking antibodies, 2A2 and 3F4 (EX1006, Abstract; EX1009, 11:21-34, FIGs. 4-15); chimeric antibodies constructed from human IgG2/G4 (EX1006, Abstract; EX1009, 8:23-26, 56-57 (human G2/G4 cDNA and amino 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).

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 including 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, as well as the two child patent applications. 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. 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 is pending and under consideration in the instant examination and reads On an antibody that binds C5 comprising a H chain SEQ ID NO: 2 and a L chain SEQ ID NO: 4.

2. Applicant's two IDSs submitted on 2/1/2017 are acknowledged and have been considered.

3. Applicant has overcome the outstanding double patenting rejection from the prior OA in light of applicant's approved TDs over 15/148,839 and 15/260,888, filed 2/1/2017.

Claim Rejections - 35 USC§ 102

4. 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:

A person shall be entitled to a patent unless -
(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.

5. Claim 1 is 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 1079.)

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 briefs, expert reports, and testimony, early in the prosecution to be considered by the Examiners.

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,[10] 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." (ALXN 2101 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 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

[10] 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.

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 '149 patent provided above reveals the similarities between that prosecution and the prosecution of the '880 patent. (*See* Section II.F.) And a review the '149 prosecution history shows that Examiner Rogers made similar rejections as in the '880 prosecution (EX1002 at 839-844; 1077-1087; 1309-1315) and that Alexion made similar arguments in response (*id*. at 1008-1013; 1248-1258; 1276-1283; 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 26-27.) 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 27.) ***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 Tacken.***

Further, the same basic combinations Samsung uses here to argue that the claimed sequences were obvious—(1) Bowdish and Evans (Ground 2); and (2) Mueller and Evans (Ground 3)—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, ¶¶ 209-247.) 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 and 17-18.

1. *Becton* Factor (c)

During prosecution of the ’880 patent and the related ’504 and ’149 patents, Examiner Rogers extensively considered the same art and arguments that Samsung rehashes in its Grounds 1-4.

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 4, relying on Bell in place of Hillmen (as do Grounds 2-3 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 1-4.

The Examiner of the ’880 patent also thoroughly considered Evans (Grounds 2-3), and reviewed other references pertaining directly to Samsung’s Grounds, including Bell (Grounds 2-4); U.S. Patent No. 7,482,435 (ALXN2016), which is cumulative of Bowdish (Grounds 1-2); and Mueller 1997, which is cumulative of Mueller PCT (Grounds 2-3). 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 the ’880 patent’s 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. 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 52-61.) 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 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 56-60.) 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 52.) 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 (ALXN2016)) 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 naturally-occurring 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 Tacken'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 Heatlh*, IPR201900573, 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, and 3 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 four Grounds meet the standard for Section 325(d), institution of Samsung's Petition should still be denied in full, because institution on all four 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 4143 (Jan. 24, 2019) (informative) (citing 35 U.S.C. § 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 '149 patent's claimed sequence.

The following table exemplifies Samsung's cited literature that described "eculizumab" as Thomas's IgG4 antibody:

Table 1: "Eculizumab" References to Thomas in Samsung's Pre-March 15, 2007 Cited Literature

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

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

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

(*See* ALXN2022, ¶¶ 122-123.)

Notably, all of Samsung's Grounds 2-4 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 7-8.) And Grounds 2-3 also include Tacken's reference to Thomas, which discloses a IgG4 antibody. That alone should be basis for non-institution.

While ***today*** SOLIRIS® (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 '149 patent's invention using hindsight knowledge of the claimed amino acid sequence—picking and choosing

from documents that a POSA would never have reviewed for information regarding the complete structure of "eculizumab." *See, e.g., Merck Sharpe & Dohme B.V. v. Warner Chilcott Co.*, 711 Fed. App'x 633, 637 (Fed. Cir. 2017) ("[U]sing the [patent-in-suit] as a roadmap to piece together various elements of [the prior art] . . . represents an improper reliance on hindsight."); *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.* 725 F.3d 1341, 1352 (Fed. Cir. 2013) ("Obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.").

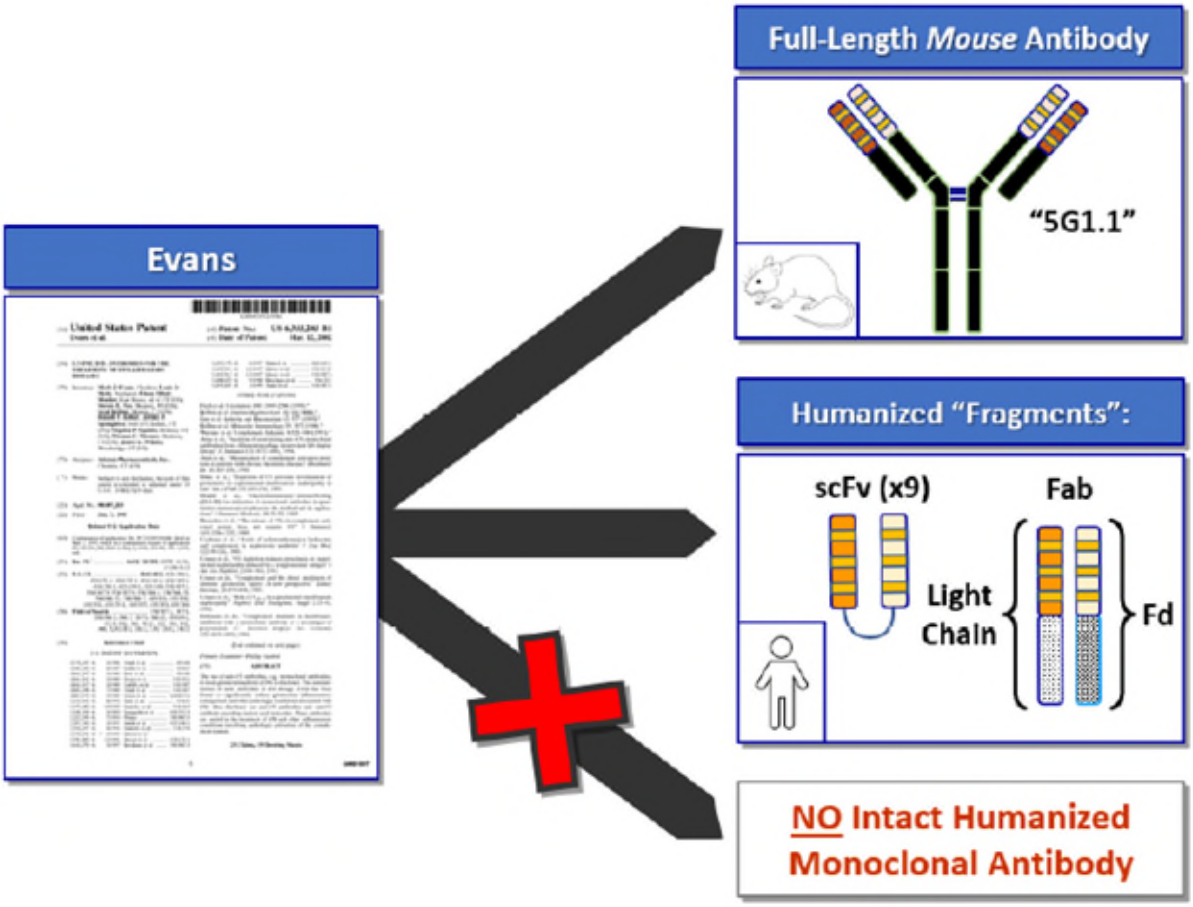
a. Evans Doesn't Teach the Claimed Sequence of "Eculizumab" or Contradict Thomas

Samsung suggests that "eculizumab" was somehow disclosed or claimed by the Evans patent (*e.g.*, Petition at 16-17, 23-26), 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 '149 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 17, 28.) Further, Evans only describes antibody constant regions generically (*e.g.*, stating that IgG constant regions are preferred), without identifying any specific heavy chain constant region

that could or should be used. (EX1005 at 45:24-33.) Nothing in Evans suggests or discloses constructing the uniquely-engineered heavy chain of the '149 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_H region, let alone the uniquely-engineered heavy chain reflected in SEQ ID NO: 2 of the '149 patent. (EX1005, Example 11; ALXN2022 ¶ 126.) For example, Evans described nine different humanized "scFv" fragments, which are recombinantly-produced molecules containing two variable regions connected by a linker, with no constant region, (EX1005, 43:6-14, 43:62-45:4), and humanized "Fab" fragments that also lack the "Fc" portion (regions C_H2 and C_H3) of an intact antibody (EX1005, 43:21-61). (ALXN2022 at ¶¶ 126, 129.) Notably, Evans' humanized Fab fragments have different heavy chain sequences ("Fd," Evans SEQ ID NOS: 11 and 12) from the claimed sequence, including in the "C_H1" constant region. (ALXN2022 at ¶¶ 126-129.) 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 (EX1004) and Mueller (EX1009) are even farther afield from the problem addressed by the '149 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 '149 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 an antibody scaffold) with a TPO receptor (the "cMpl receptor"), a biological interaction that is not part of the complement pathway. (EX1004 ¶ [0192].) Samsung does not and cannot explain why a POSA seeking a safe and effective anti-C5 antibody would have looked to Bowdish. *See, e.g.*, *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013).

Likewise, Mueller PCT, and the associated Mueller 1997, concerned an issue unrelated to the '149 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 8-10.) 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 7 (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 16-17 (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 7 (citing EX1010)). And even in its hindsight effort to connect the

broad terms "5G1.1" or "h5G1.1" with "eculizumab," Samsung relies on documents that identified "eculizumab" as Thomas's IgG4 antibody. (*See, e.g.*, Petition at 5-7.) Thus, neither Bowdish's reference to using "5G1.1" as a scaffold for a TPO-mimetic peptide (EX1004 ¶¶ [0066], [0191]), nor Bowdish's citation to Evans (*id*. ¶ [0191]), would have explained to a POSA how Bowdish's TPO-mimetic construct relates to the structure of "eculizumab," including the structure of its heavy chain constant region (ALXN2022, ¶¶ 212, 219).

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 isotope 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 the antibody structure described in Thomas in exchange for a uniquely-engineered antibody with unknown efficacy and safety.

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

A POSA as of March 15, 2007 would not have had any motivation to alter the structure of "eculizumab" described in the art at that time, and would not have reasonably expected success in doing so. As discussed above, a POSA would have understood "eculizumab," the antibody reported as preventing cleavage of C5 and safely and effectively treating patients with PNH, to be Thomas's IgG4 antibody. (*See* Sections II.C, 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* Sections 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, ¶¶ 107-117.) 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_H 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 (summarizing studies from before March 15, 2007, and explaining how heavy chain isotype switching "is associated with altered specificity despite conservation of [the variable] region sequence").) In particular, the art described how changes to the "C_H1" and "hinge" portions of the heavy chain could significantly impact antigen-affinity and specificity, even without changes to the variable region. (*See, e.g.*, ALXN2012 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 a IgG2/4 hybrid sequence, could present heightened immunogenicity concerns. In particular, a POSA would have known that administering an antibody with a "foreign" heavy chain isotype to human patients could potentially result in harmful immunogenic reactions. (*See, e.g.*, ALXN2015 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 isotype—would have been motivated to create a novel antibody with potentially different clinical properties by instead using the uniquely-engineered heavy chain reflected in SEQ ID NO: 2. Nor can Samsung explain how a POSA would have reasonably expected to succeed in using an antibody that deviated from the "eculizumab" structure suggested by the prior art.

Crucially, as of March 15, 2007, there was not a single FDA-approved monoclonal antibody product featuring the uniquely-engineered heavy chain of SOLIRIS® (*see*, *e.g.*, EX1044 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®—first approved ***after*** March 15, 2007—was the ***first*** FDA-approved antibody with its uniquely-engineered C_H region.

V. A PERSON OF ORDINARY SKILL IN THE ART

Alexion does not dispute Samsung's POSA definition (Petition at 12-13), 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 claim 1 of the '149 patent under any of its four fatally flawed Grounds.

VI. SAMSUNG FAILS TO SHOW UNPATENTABILITY OF ANY CHALLENGED CLAIM

A. Samsung's Ground 1 Fails Because It Cannot Show Bowdish Anticipated Claim 1

Samsung's Ground 1 contends that claim 1 was anticipated by Bowdish. But Bowdish alone does not disclose the claimed sequence. And Bowdish's limited incorporation by reference of Evans' 5G1.1, the parental mouse monoclonal antibody, and the only full antibody sequence disclosed in Evans, would direct a POSA to a murine framework sequence, not the claimed sequence.

In sum, Samsung's Ground 1 overreaches by incorrectly contending that Bowdish discloses the sequence of "eculizumab." A POSA would not have recognized ***any*** disclosure in Bowdish of the antibody having SEQ ID NOS: 2 and 4. Bowdish disclosed neither "eculizumab" nor any other C5-binding antibody. And even Samsung admits that Bowdish plainly does not disclose the heavy chain CDR3 of the claimed sequence. (Petition at 16.) Samsung's argument ignores Bowdish's incorporation-by-reference of Evans' 5G1.1 murine framework region and its ***lack*** of incorporation of any other sequences to make its "anticipation" argument. Accordingly, Samsung's Ground 1 overreaches and fails.

Samsung relies on a statement appearing in Example 4 of Bowdish: "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.[11]) Notably, the statement does not incorporate any of Evan's scFv sequences, including the HCDR3 sequence admittedly missing from Bowdish. Thus, Bowdish cannot anticipate. (*See* ALXN2022, ¶¶ 187-194.)

Contrary to Samsung's suggestion (Petition at 23), Bowdish does not "explain[] that it created SEQ ID NO:67 from a starting chain sequence that is identical to SEQ ID NO:2." It makes no reference to "eculizumab" at all, and rather references Evans' heavy chain of the murine 5G1.1 sequence. (EX1004, ¶ 191.) Nor does Bowdish identify the "native CDR3" of Evans' antibody as

[11] In IPR2019-00741, 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 "5G1.1" mouse antibody sequence incorporated by reference into Bowdish. As Dr. Casadevall 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, ¶¶ 188-191, 214-215.)

"eculizumab" or any other specific sequence. (Petition at 23.) Thus, Samsung's anticipation story and after-the-fact sequence comparisons (Petition at 24) are just hindsight obviousness arguments using the claims as a roadmap.

B. Samsung's Ground 2 Fails Because It Cannot Show that Claim 1 Is Obvious Over Bowdish and Evans in View of Bell, Tacken, and Mueller PCT

Samsung's Ground 2 fails because Samsung cannot show how, without hindsight, a POSA would have been motivated to select and combine Bowdish and Evans, in view of Bell, Tacken, and Mueller PCT to obtain the claimed invention, or how they could have reasonably expected to succeed in doing so.

Samsung relies on impermissible hindsight bias, which the Supreme Court and the Federal Circuit have repeatedly warned against in evaluating obviousness. *See, e.g.*, *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966); *Monarch Knitting Mach.*, 139 F.3d at 881 ("Defining the problem in terms of its solution reveals improper hindsight in the selection of prior art relevant to obviousness."); *Zoltek Corp. v. U.S.*, 815 F.3d 1302, 1313 (Fed. Cir. 2000) (warning against "the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher"). Here, Samsung uses its present-day knowledge of the SOLIRIS® antibody claimed in the '149 patent to reconstruct its uniquely-engineered, non-naturally occurring amino acid sequence from bits and pieces of

art, including the non-analogous "Bowdish" reference that a POSA without hindsight would have never considered. At the same time, Samsung ignores the art's consistent teaching that "eculizumab" had an IgG4 constant region as described in Thomas—which ***taught away*** from the claimed invention. For this reason, Samsung's Ground 2 must fail.

Samsung cannot explain why a POSA seeking to develop an anti-C5 antibody would ever have started with Bowdish—a reference having nothing to do with blocking C5 cleavage or treating PNH. *See Broadcom*, 732 F.3d at 1334 (affirming nonobviousness finding where the asserted art and the patent-in-suit "addressed two different problems"). Bowdish is not analogous art to the '149 patent. *See, e.g., Circuit Check Inc. v. QXQ Inc.,* 795 F. 3d 1331, 1335 (Fed. Cir. 2015) ("[D]isputed prior art can be analogous only if it is reasonably pertinent to the particular problem solved by the inventor."). Bowdish's TPO-mimetic constructs were not tested for, and were not intended to have, anti-C5 activity or efficacy in treating PNH; and the TPO activity of these constructs had nothing to do with the complement pathway or C5. Without hindsight, a POSA would have had no reason to "look to [Bowdish] to solve the particular problem at hand" that was solved by the invention of the '149 patent. *Circuit Check*, 795 F.3d at 1335.

Further, there is no basis for Samsung's hindsight-driven contention that a POSA would have reverse-engineered "eculizumab" by substituting a heavy chain CDR3 sequence from Evans into the TPO-mimetic construct of Bowdish. *See, e.g.*, *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019) ("[W]orking backwards from [a] compound, with the benefit of hindsight, once one is aware of it does not render it obvious."). Neither Bowdish nor Evans mentioned "eculizumab"—and Samsung's assertions to the contrary further confirm its reliance on impermissible hindsight. (*See* Section 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 wide variety of possible murine and humanized antibodies and fragments, and that was in no way limited to "eculizumab." (*See* Section IV.A.2.b.) Evans, in turn, described only variable region fragments of anti-C5 antibodies, and did not describe the constant region of "eculizumab" or any other complete humanized anti-C5 antibody. (*See* Section 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 all of them. (Petition at 36.) But a POSA without hindsight would have had ***no reason*** to believe that combining Bowdish's TPO-mimetic construct with one of the many

sequences from Evans would lead to "eculizumab." (*See* ALXN2022, ¶¶ 183-220.)

Samsung exacerbates its hindsight error by ignoring what the art (including Bell) ***actually*** taught a POSA as of March 15, 2007 about the structure and sequence of "eculizumab": that it was consistently described by referencing Thomas, which disclosed an IgG4 isotype antibody. (*See* Table 1.) Samsung cannot explain why a POSA, without the benefit of hindsight, would have ignored the clear teachings of the art regarding the structure of "eculizumab," and instead turned to non-analogous art such as Bowdish to experiment with different antibody sequences that were ***not*** known to prevent C5 cleavage or safely and effectively treat PNH, and had not been studied in humans. Rather, the art's teaching that "eculizumab" had the IgG4 structure described in Thomas ***taught away*** from such unwarranted, unpredictable experimentation with the TPO-mimetic constructs of Bowdish (*see* ALXN2022, ¶¶ 223-229). *Millennium Pharm.*, 862 F.3d at 1366.

Even if Bowdish and Evans were combined as per Samsung's hindsight-driven theory, a POSA would not have reasonably expected the resulting compound to work at preventing C5 cleavage and safely and effectively treating PNH. *See*, *e.g.*, *Novartis Pharm. Corp. v. West-Ward Pharms. Int'l Ltd.*, No. 2018-1434, 2019 WL 2079879, *7-8 (Fed. Cir. May 13, 2019). A POSA would

have understood that even small changes to the amino acid sequence could have a substantial impact on the binding properties and the safety and efficacy of an antibody. (*See* Section IV.A.) A POSA would not have reasonably predicted the activity, safety, or efficacy of the antibody that Samsung cobbles together in hindsight from Bowdish and Evans, which differs significantly from Thomas's IgG4 antibody described in the art as "eculizumab." Nor was there any reason for a POSA to undertake extensive testing of such an antibody, when the art taught that "eculizumab" (*i.e.*, the IgG4 antibody described in Thomas) was already thoroughly studied and shown to be a clinical success. (*See* ALXN2022, ¶ 228, Figure 13.) Notably, if consulted, both Bell and Tacken cited by Samsung in this Ground would also have led the POSA to the IgG4 antibody described in Thomas.

Mueller, as an anti-VCAM reference, would not even have been consulted. But if it had been, Mueller also would have pointed the other way. As the Board previously noted in IPR2019-00740, Mueller identified ***only*** an ***IgG4*** isotype antibody (*i.e.*, the isotype of Thomas) as an "anti-C5 antibody," and taught nothing about the C5 binding or clinical properties of "h5G1.1 CO12 HuG2/G4 mAb." (Paper No. 15 at 57.)

Samsung's proposed sequence comparisons (Petition at 31-32) and "routine alignments" (Petition at 31) are again, the epitome of hindsight. A POSA would

have had to work back from the claimed sequence to make any sense of these comparisons and alignments and would never have been motivated to make them in the first place given the disparate nature of the references: Bowdish (TPO-mimetic peptides), Mueller (anti-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 32) except with the benefit of hindsight and by ignoring the reference to Evans' 5G1.1 murine antibody.[12]

As Samsung cannot show obviousness of claim 1 of the '149 patent over Bowdish and Evans, in view of Bell, Tacken, and Mueller PCT, Ground 2 fails the standard for institution.

C. Samsung's Ground 3 Fails Because It Cannot Show that Claim 1 Is Obvious Over Evans and Mueller PCT in View of Bell and Tacken

Samsung attempts to combine Evans and Mueller PCT "in view of Bell and Tacken" to arrive at the claimed sequence. But again, the only actual antibody disclosed in Evans is the 5G1.1 murine antibody and Mueller relates to an entirely

[12] Samsung admits that Evans discloses "the original mouse antibody 5G1.1, which binds C5." (Petition at 35.)

different antibody directed at "VCAM." As the Board previously noted in IPR2019-00741, Mueller identified ***only*** an ***IgG4*** isotype antibody (*i.e.*, the isotype of Thomas) as an anti-C5 antibody, and taught nothing about the C5 binding or clinical properties of "h5G1.1 CO12 HuG2/G4 mAb." (IPR2019-00741 (Paper No. 15 at 53-54).)

Nor would a POSA have been motivated to combine the sequences in Evans and Mueller—neither of which cites to each other—in the exact manner to get the specific claimed antibody sequence of the '149 patent. As the Board previously concluded: "We are left asking why would the skilled artisan pair Evans and Mueller, and then chose [sic] precisely the portions of Evans's and Mueller's disclosed amino acid sequences to use and which to discard so as to arrive at a final antibody that perfectly matched the claimed antibody?" (IPR2019-00741 (Paper No. 15 at 53-54).)

Just as in Ground 2, even if a POSA were somehow motivated to combine these disparate references, viewing them in light of the Bell and Tacken references of Ground 3 would have led the POSA even further astray as both of those references cited to Thomas's HuG4 sequence for the sequence of the anti-C5 antibody eculizumab.

Mueller also did not include any experiments or data on C5 binding, blocking C5 cleavage, or treating PNH. Insofar as Mueller described "h5G1.1" antibodies, with either IgG4 or "IgG2/G4" heavy chain constant regions, these were exclusively used as "isotype control" antibodies in studies measuring the activity of the anti-VCAM antibodies. (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" for its *in vitro* experiments, as long as it did not bind to VCAM. Ultimately, the Board concluded that "[i]t is not apparent that the skilled artisan, knowing of Evans, would look to Mueller, or vice versa." (IPR2019-00741, Paper 15 at 54.)

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

POSA would not have reasonably expected to still block C5 cleavage or be safe or effective for human administration to treat PNH. (*See* ALXN2022, ¶¶ 233-252.) In fact, a POSA as of March 15, 2007 would not have known of ***any*** human clinical testing reporting the safety of antibodies using the "IgG2/G4" hybrid described in Mueller, which only featured *in vitro* experiments.

Samsung again attempts to support its argument with hindsight sequence alignments and comparisons. (Petition at 37-39) It picks and chooses a specific variable sequence from Evans' Example 11, identified as "CO12," combines it with the constant G2/G4 regions of Mueller PCT, and then compares it to the claimed sequences to argue obviousness. But nothing in Evans or Mueller 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 combination is pure hindsight. (IPR2019-00741, Paper 15 at 54; *see also* ALXN2022, ¶¶ 236-252.)

D. Samsung's Ground 4 Fails Because It Cannot Show that Claim 1 Is Anticipated by Bell

Samsung's Ground 4 fails because Bell does not expressly or inherently disclose all the elements recited in claim 1 of the '149 patent. *See, e.g.*, *Therasense, Inc. v. Becton Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) ("Anticipation requires the presence in a single prior art disclosure of all elements

of a claimed invention arranged as in the claim."). Samsung openly admits that "Bell's disclosure does not include the exact amino acid sequence of eculizumab . . ." (Petition at 28.)

In circular fashion, Samsung merely restates its hindsight obviousness arguments in the guise of "enablement" to argue that Bell "inherently" disclosed the claimed sequence. (Petition at 44.) But neither this sleight of hand nor the supposed "admission" that "it is known today that SOLIRIS® as used in these studies had the claimed sequence of SEQ ID NOS: 2 and 4[.]" (Petition at 42) can change the fact that the sequence was ***unknown*** at the time of Bell's publication and was disclosed there as corresponding to Thomas's IgG4 isotype.

Significantly, Bell fails to disclose at least the element of "a heavy chain consisting of SEQ ID NO: 2." While Bell described administering "eculizumab" for treating PNH, ***nothing*** in Bell taught the uniquely-engineered heavy chain reflected in "SEQ ID NO: 2." (*See* Section VI.A.) Rather, Bell referenced Thomas's ***IgG4*** antibody that is different sequence than that of SEQ ID NO: 2. In particular, Bell cited Thomas as describing "[m]ethods for the preparation of h5G1.1-mAb . . . under the tradename eculizumab"[13] (EX1007 ¶ [0052]), and

[13] While paragraph [0052] of Bell also cited Evans for the disclosure of

described positive Phase II clinical results for "eculizumab" in PNH patients (EX1007 ¶¶ [0081]-[0095]). Bell thus would have further taught away from other antibody constructs that lacked such published reports of clinical safety and efficacy, such as the uniquely-engineered, non-naturally occurring antibody claimed in the '149 patent.

Accordingly, nothing in Bell discloses each and every element of claim 1 of the '149 patent. Nor could Bell have enabled a POSA to make and use the specific antibody recited in claim 1 without undue experimentation, because Bell (and all of the other art) guided a POSA to make and use a very different antibody—Thomas's ***IgG4*** isotype antibody. *See, e.g.*, *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) (for a reference to anticipate, "[i]t is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation"). (*See* ALXN2022, ¶¶ 204-208.)

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

Samsung implicitly concedes that Bell did not disclose or enable the invention of claim 1, because Samsung's theory of "enablement" requires a POSA to combine bits and pieces of the claimed sequence from various other prior art documents, including, *e.g.*, Evans, Bowdish, Mueller, and Tacken. (*See* Petition at 44-45.) Samsung's "enablement" arguments appear simply to be a restatement of the obviousness arguments that Samsung asserts under Grounds 2 and 3 and, which Samsung has improperly attempted to shoehorn into an alleged anticipation argument. *See, e.g.*, *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002) ("[A]nticipation requires that each limitation of a claim must be found in a single reference . . . [and] does not permit an additional reference to supply a missing claim limitation."). In any case, Samsung has failed to show that a POSA provided with Bell and the Evans, Bowdish, Mueller, or Tacken references as of March 15, 2007 would have been led to the '149 patent's claimed amino acid sequence without undue experimentation, when Bell, and the many other references listed in Table 1 taught a POSA that "eculizumab" was Thomas's IgG4 antibody. (*See* Section IV.A.1.)

Acknowledging that Bell failed to expressly disclose the amino acid sequence recited in claim 1 of the '149 patent, Samsung is forced to turn to non-prior art, post-filing information regarding the sequence of SOLIRIS®, and

attempts to read that information back into the prior art under the guise of alleged "inherent anticipation." (*See, e.g.*, Petition at 41-43.) As explained below, however, Samsung's inherent anticipation theory fails because it is premised on both a misapplication of the law and a misstatement of the pertinent facts.

In particular, Samsung alleges inherent anticipation of claim 1 on the grounds that ***today***—years after the '149 patent's March 15, 2007 priority date—it is known that the clinical study underlying the Bell publication ***actually*** used an antibody with a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4. But Samsung is mistaken on the law. The mere naming of an investigational product (*e.g.*, "eculizumab") in a prior art publication does ***not*** inherently anticipate later-filed patent claims detailing the specific structure or composition of that product (*i.e.*, SEQ ID NOs: 2 and 4), if a POSA could not have ***necessarily*** determined the later claimed structure/composition from the information publicly available as of the priority date. *See, e.g., Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-83 (Fed. Cir. 2018). Likewise, post-filing information showing that the later-claimed antibody sequence was actually used in the studies underlying prior art clinical publications is insufficient to give rise to inherent anticipation, especially when those prior art publications would have guided a POSA to a different sequence. *See, e.g.*, *id.*;

Bayer CropScience LP v. Syngenta Ltd., IPR2017-01332, Paper 15 at 3-6 (Apr. 2, 2018).

Accordingly, even if it is known today that the "eculizumab" antibody used in the clinical studies underlying the Bell publication was in fact the antibody recited in claim 1, Samsung has not shown inherent anticipation of that claim. That is because Samsung fails to show that a POSA as of March 15, 2007 reading Bell would have ***necessarily*** known that the antibody used in those studies had the later-claimed amino acid sequence. *See Endo*, 894 F.3d at 1378-83. To the contrary, as discussed above, a POSA reading Bell would have envisioned that the antibody "eculizumab" was a very different antibody than what the '149 patent claims, having Thomas's "IgG4" heavy chain rather than the unique, non-naturally occurring heavy chain region reflected in "SEQ ID NO: 2." (*See* Section IV.A.1.) A publication's use of the name "eculizumab" to refer to an antibody used in a clinical study does not constitute disclosure of the actual sequence of that antibody, particularly when a POSA as of March 15, 2007 would have understood that name to refer to a different sequence (*i.e.*, the sequence set forth in Thomas). *See, e.g.*, *Bayer CropScience*, IPR2017-01332, Paper 15 at 3-6.

Nor could a POSA as of the priority date have independently determined the sequence of the antibody clinically tested in Bell. Rather, as discussed in the

Boone Declaration during prosecution of the '149 patent (EX1002 at 1252-1254), 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.)

Moreover, a POSA attempting to determine the sequence of "eculizumab" as described in Bell would have followed that publication's reference to Thomas and arrived at the IgG4 antibody that Thomas described—an antibody having a very different sequence than the one recited in claim 1 of the '149 patent. (*See* Section IV.A.1.)

Alexion's so-called admissions that the claimed sequence was known before 2007 are neither here nor there. What matters is what the art actually taught, not whether it was correct or what Alexion inadvertently incorrectly said about it. The fact is that as of March 15, 2007, the art consistently taught that the sequence of eculizumab had an IgG4, ***not*** the sequence of claim 1.

Samsung incorrectly relies on *In re Crish*, 393 F.3d 1253, 1256 (Fed. Cir. 2004), which is distinguishable on the facts here. (Petition at 41.) *In re Crish* involved a scenario where a POSA provided with the alleged anticipating reference could have readily determined the claimed DNA sequence of a "known," naturally-occurring DNA segment (a "promoter region") by applying common DNA-

sequencing techniques to a publicly available plasmid identified in the prior art. The claimed promoter region was not "new" because the gene was known, had been used years before, and the promoter region was identified in the prior art plasmid by size and location—thus allowing a POSA to readily determine the sequence of the promoter region without undue experimentation. *See In re Crish*, 393 F.3d at 1258.

With respect to Bell, in contrast to the facts of *In re Crish*, "eculizumab" was not a "known" antibody for which the sequence could have been determined. *See Endo*, 894 F.3d at 1378-79. As the Boone Declaration explained, the identity of the sequence and composition of the antibody product used in the clinical trials published as Bell was confidential. No one outside of Alexion (or those bound in confidentiality to Alexion) knew the actual sequence of "eculizumab," nor could they have obtained the antibody for sequencing. Moreover, a POSA attempting to determine the sequence of "eculizumab" as described in Bell would have followed those publications' references to Thomas and arrived at the IgG4 antibody that Thomas described—an antibody having a very different sequence than the one recited in claim 1 of the '149 patent. (*See* Section IV.A.1.) Accordingly, *In re Crish* does not merit a finding that Bell inherently anticipates claim 1 of the '149 patent.

As Samsung cannot show the presence of all of the elements of claim 1 in Bell, Ground 4 fails the standard for institution.

E. The Objective Indicia of Non-Obviousness Support Validity

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

SOLIRIS®, the commercial embodiment of the '149 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® 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 at 70.) The outstanding economic performance of SOLIRIS® has a direct nexus to the patented features of the '149 patent, which claims the uniquely-engineered, non-naturally occurring antibody responsible for the drug's clinical (and therefore commercial) success as a treatment for PNH. *See, e.g., Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392-93 (Fed. Cir. 1988).

The introduction of SOLIRIS® also fulfilled a long-felt, unmet need in the market, as the first FDA-approved treatment to reduce hemolysis in patients with PNH—demonstrated by the FDA and the EU granting SOLIRIS® "orphan drug" status for PNH. (ALXN2019 at 1270.) *See, e.g.*, *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994, 997-998 (Fed. Cir. 2009). SOLIRIS® also received industry praise as the recipient of multiple Prix Galien awards (the industry's highest accolade for pharmaceutical research and development), including the Prix Galien USA 2008 Award for Best Biotechnology Product, and the Prix Galien France 2009 Award for Most Innovative Drug for Rare Disease. (ALXN2020; ALXN2021.)

Samsung says that its intent to develop a biosimilar copy of SOLIRIS® should not count as secondary evidence of non-obviousness because it is required by statute and regulation to make a product highly similar to the reference product. (Petition at 48.) This is not so. Samsung, Amgen, and at least two other sophisticated pharmaceutical companies could have chosen to develop biosimilars of any of hundreds of other biologic products. (*See, e.g.*, clinicaltrials.gov.) Instead, they chose to copy SOLIRIS®.

Samsung's denial of the existence of secondary considerations of non-obviousness is just a rehashing of its prior art obviousness arguments. (Petition at

45-48.) 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 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 indica 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, ALXN2007-2013, ALXN2015-2022, ALXN2026, ALXN2098, ALXN2100-2103** were served via electronic mail on September 12, 2023, in their entirety on the following:

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CERTIFICATION OF WORD COUNT

The undersigned hereby certifies that the portions of the above-captioned **PATENT OWNER'S PRELIMINARY RESPONSE** specified in 37 C.F.R. § 42.24 has 13,492 words, in compliance with the 14,000 word limit set forth in 37 C.F.R. § 42.24. This word count was prepared using Microsoft Word.

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