UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

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Case No. IPR2019-00740
Patent: 9,718,880

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

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TABLE OF CONTENTS

Table of Contents
(continued)

Page

TABLE OF AUTHORITIES

Cases

Statutes

Rules

EXHIBIT LIST

Exh. No.	Description
2001	Declaration of Evan D. Diamond in support of Motion for *Pro Hac Vice*
2002	Evan D. Diamond Biography
2003	Declaration of Vanessa Y. Yen in support of Motion for *Pro Hac Vice*
2004	Vanessa Y. Yen Biography
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2008	McCloskey *et al.*, Human Constant Regions Influence the Antibody Binding Characteristics of Mouse-Human Chimeric IgG Subclasses, IMMUNOLOGY, 88: 169-173 (1996)
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2012	Pritsch *et al.*, Can Isotype Switch Modulate Antigen-Binding Affinity and Influence Clonal Selection?, EUR. J. IMMUNOL., 30: 3387-95 (2000)
2013	McLean *et al.*, Isotype Can Affect the Fine Specificity of an Antibody for a Polysaccharide Antigen, J. OF IMMUNOLOGY, 169: 1379–86 (2002)
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I. INTRODUCTION

Alexion provides the following Preliminary Response to Amgen's Petition seeking review of claims 1-3 of Alexion's U.S. Patent No. 9,718,880 ("the '880 patent"). The Board should deny Amgen's Petition because each of its Grounds is fatally flawed and fails to prove that the challenged claims are unpatentable.

In particular, each of Amgen's six "Grounds" is based on a mistaken premise – that a person of ordinary skill in the art ("POSA") would have known the specific amino acid sequence of the uniquely-engineered monoclonal antibody recited in the claims of the '880 patent and commercialized as Alexion's groundbreaking orphan disease therapy known today as SOLIRIS®. Prior to March 15, 2007, the priority date of the '880 patent, however, the unique amino acid sequence of SOLIRIS® was not publicly known or disclosed in the prior art. Amgen's arguments to the contrary are concocted from prior art that the Examiner of the '880 patent already considered, and that Amgen deliberately selected and combined using hindsight knowledge of the '880 patent's invention and its clinical and commercial success.

Claims 1-3 of the '880 patent generally cover pharmaceutical compositions of the previously undisclosed, uniquely-engineered anti-C5 therapeutic antibody in SOLIRIS®, as defined by its specific amino acid sequence. SOLIRIS®, also referred to today by its non-proprietary name "eculizumab," is a first-in-class

treatment for patients with the rare, potentially fatal blood disease paroxysmal nocturnal hemoglobinuria ("PNH"), caused by red blood cells losing their normal protection against the "complement" immune pathway. SOLIRIS® works by binding to component 5 ("C5") of the complement pathway and preventing its cleavage into components "C5a" and "C5b," which mediate downstream effects of the complement pathway, including bursting of red blood cells ("hemolysis") in patients with PNH.

Amgen cannot show any teaching in the prior art that would have led a POSA to the uniquely engineered, non-naturally occurring sequence of SOLIRIS® recited in the claims of the '880 patent. Amgen does not dispute that, prior to March 15, 2007, no single document disclosed the entire amino acid sequence in SOLIRIS®. Nor does Amgen contend that SOLIRIS® was available to the public for testing or analysis prior to that date.

If a POSA were searching for the sequence of "eculizumab" as described in the art, the literature as of March 15, 2007 identified an amino acid sequence and corresponding structure that is very different from what the '880 patent claims. In particular, publications describing the safety, efficacy, and clinically relevant biological activity of "eculizumab" consistently directed a POSA to the 1996 "Thomas" publication (AMG1023) for the structure and design of the antibody, which in turn described a humanized antibody constructed with a naturally-

occurring "***IgG4***" heavy chain constant region. The claimed antibody of the '880 patent has a very different, uniquely-engineered, non-naturally occurring constant region that was nowhere described in Thomas or the prior art literature showing the safety and efficacy of "eculizumab."

Amgen's Grounds 1-4 thus fail because they incorrectly presume that Hillmen 2004 (AMG1004) and Hill 2005 (AMG1047) disclosed the claimed sequence of the '880 patent, when in fact, they described "eculizumab" by referencing the ***IgG4 antibody of Thomas***. By disregarding Hillmen's and Hill's clear teaching directing a POSA to Thomas's antibody – which even the Examiner of the '880 patent properly recognized after evaluating Hillmen during prosecution – Amgen uses improper hindsight.

Amgen's Grounds 5 and 6 also fail, because they rely on hindsight knowledge to reconstruct the claimed sequence of the '880 patent from bits and pieces of unrelated, non-analogous prior art. Such hindsight-driven analysis is always an improper basis for alleging obviousness. *See, e.g.*, *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (warning against "slipping into use of hindsight" and "the temptation to read into the prior art the teachings of the invention in issue"); *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2017) (warning against

"the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning").[1]

In particular, Amgen uses hindsight to cobble together the claimed sequence of the '880 patent from Bowdish (AMG1006) or Mueller (AMG1008) (for portions of the claimed sequence, including its non-natural heavy chain constant region), and Evans (AMG1007) (for the variable region of the claimed sequence). But Amgen fails to show why a POSA ***without*** hindsight would have selected Bowdish or Mueller and combined them with Evans to obtain the claimed antibody of the '880 patent, or how they could have reasonably expected success in doing so.

Critically, ***nowhere*** did Bowdish or Mueller even use the word "eculizumab." Nor did Bowdish or Mueller address the problem of the '880 patent – development of a monoclonal antibody that prevents C5 cleavage and is safe and effective for treating PNH. Despite acknowledging that "[a] POSA is presumed to be aware of all the pertinent prior art" (*e.g.*, Petition at 55), Amgen disregards the art's ***actual*** teachings about the structure and sequence of "eculizumab" in favor of a convoluted theory that improperly picks and chooses from non-analogous art in hindsight.

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

A POSA without hindsight also would not have reasonably expected success in combining Bowdish or Mueller with Evans and the Bell (AMG1005) and Wang (AMG1028) references. Bell, like Hillmen and Hill, taught a POSA as of March 15, 2007 that "eculizumab" had the ***IgG4*** constant region of Thomas; and nothing in Bowdish, Mueller, Evans or Amgen's other cited art would have given a POSA a reasonable expectation that an antibody with a different, non-naturally occurring constant region – with no published reports indicating that such a constant region had been tested in humans – would be safe and effective to block C5 cleavage and treat conditions such as PNH. A POSA also would not have reasonably expected that substituting such a uniquely-engineered constant region would allow the antibody to retain the anti-C5 activity and therapeutic efficacy of "eculizumab" as reported in the literature. To the contrary, it was well-known as of 2007 that changes to the amino acid sequence of a monoclonal antibody (including in the heavy chain constant region) could significantly alter antibody properties including affinity, specificity, and immunogenicity, which could translate into unwanted clinical differences *in vivo*.

Amgen also fails to show any prior art teaching of the elements "300 mg single-use dosage form" or "30 ml of a 10 mg/ml [anti-C5] antibody solution" recited in '880 patent claims 1 and 3. For example, Amgen concedes that none of its cited art disclosed an antibody with the claimed sequence of the '880 patent in a

"300 mg single-use dosage form" or a "10 mg/ml antibody solution"; and Amgen fails to show how a POSA without hindsight would have otherwise arrived at that specific pharmaceutical composition.

As Amgen fails to show that any of the challenged claims were unpatentable, Amgen's request for institution must be denied. *See* 35 U.S.C. § 314(a); 37 C.F.R. § 42.108(c). Institution should also be denied because the Examiner already extensively considered and rejected the majority of Amgen's alleged Grounds during prosecution, and also reviewed documents cumulative of those raised in Amgen's remaining Grounds in the course of finding claims 1-3 of the '880 patent to be novel and nonobvious over the prior art. *See* 35 U.S.C. § 325(d).

II. BACKGROUND

A. SOLIRIS® and its Use to Treat PNH

The challenged claims of the '880 patent generally cover pharmaceutical compositions of a non-naturally occurring, uniquely-engineered humanized monoclonal 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* AMG1033 at 1256; ALXN2005 at 1.)

PNH is a rare, life-threatening blood disorder characterized by chronic hemolysis, which leads to severe anemia requiring transfusions, disabling fatigue,

blood in the urine ("hemoglobinuria"), impaired quality of life, recurrent pain, kidney failure, and blood clotting ("thrombosis"). (AMG1047 at 2559, 2564; AMG1005 ¶ [0005].) PNH is caused by a genetic mutation resulting in abnormal blood cells that are unprotected from the body's "complement" system – a component of the human immune system that normally protects the body against invading infectious cells (*e.g.*, pathogenic bacteria), but when unimpeded, can attack the body's own cells and cause deleterious effects. (AMG1033 at 1256-1257.) In PNH patients, red blood cells are exquisitely sensitive to destruction by the complement system, and are constantly under attack, with periodic episodes of hemolysis ("paroxysms") that can be triggered by factors such as infections or strenuous exercise. (AMG1033 at 1259.)

Prior to FDA approval of SOLIRIS®, therapies for PNH included blood transfusion, erythrocyte-stimulating agents, corticosteroids, anabolic steroids, oral iron therapy, and bone marrow transplantation. (ALXN2006 at 994.) PNH patients were often dependent on frequent blood transfusions for survival. (AMG1047 at 2559.) In clinical trials of SOLIRIS®, PNH patients showed reduced hemolysis and substantial improvements in outcomes, including reduced or eliminated need for blood transfusions, lessened anemia and fatigue, and improved quality of life. (AMG1033 at 1261.) Those trials also confirmed the safety of SOLIRIS® for long-term administration. (AMG1047 at 2564.)

SOLIRIS® works by binding with high "affinity" (*i.e.*, tightness) and "specificity" (*i.e.*, directed to a single target or "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* AMG1033 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; AMG1018 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 and a portion of the heavy chains, denoted V_L and V_H, respectively. (ALXN2007 at 105-06.) Likewise, the constant region is comprised of a portion of the light chains and a

portion of the heavy chains, denoted C_L and C_H, respectively. (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. (AMG1018 at 9.) Portions of the variable region flanking the CDRs are termed "framework" regions. (AMG1029 at 6.)

Five different classes of naturally-occurring antibodies – IgA, IgD, IgE, IgG, and IgM – can be distinguished by their constant regions. (ALXN2007 at 105; AMG1018 at 4-7; AMG1029 at 5.) IgG is the most abundant in humans, and as of March 15, 2007, was the most common class used for human therapy. (ALXN2007 at 105; AMG1018 at 4; AMG1029 at 2-5.) As depicted in Figure 1 (adopted from Amgen's Petition), IgG constant regions can be subdivided into different parts, including a light chain constant region C_L, and heavy chain constant regions CH1, the "hinge" region, CH2, and CH3.

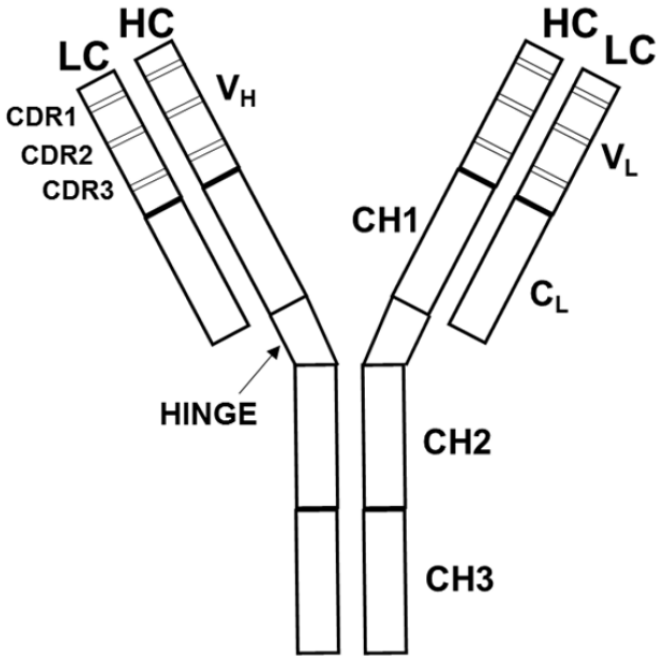


Figure 1: Basic structure of an IgG antibody

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; AMG1029 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* AMG1029 at 5.) As of March 15, 2007, humanized monoclonal antibodies approved by the FDA were predominantly of the naturally-occurring IgG1 or IgG4 isotypes. (*See, e.g.*, AMG1029 at 2-4, Table 1.)

As of March 15, 2007, it was understood that the three-dimensional structure of an antibody was critical to its ability to selectively bind a target antigen. (ALXN2007 at 109-10.) Accordingly, a POSA would have understood that changes in an antibody's sequence could potentially affect its affinity and specificity, and thus, its safety and efficacy in humans. (*See, e.g.*, AMG1040 at 34; ALXN2010 at 3; ALXN2011 at 2240-42; ALXN2008 at 171-72; ALXN2012 at 3391-92; ALXN2013 at 1384-86; ALXN2009 at 13924-26.) A POSA would have known that antibody affinity and specificity could be substantially influenced even by sequence changes outside of the antigen-binding site, *e.g.*, in the heavy chain constant region. (*See, e.g.*, ALXN2014 at 226-27.) A POSA would have also understood that such sequence changes could potentially result in harmful immunogenic reactions following human administration. (*See, e.g.*, ALXN2015 at 508 (single amino acid substitution in an antibody drastically impacted how other antibodies ("anti-idiotype" antibodies) would bind to it).)

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. (AMG1004 at 552, 558;

AMG1047 at 2559, 2564; AMG1012 at 1239, 1241-1242.) But a POSA at that time would ***not*** have known that "eculizumab" had the sequence claimed in the '880 patent, including the uniquely-engineered heavy chain constant region reflected in "SEQ ID NO: 2." Rather, the literature taught a POSA that "eculizumab" contained an "***IgG4***" heavy chain constant region – a ***very different*** structure and amino acid sequence from "SEQ ID NO: 2" of the '880 patent.

Specifically, the literature as of March 15, 2007 consistently directed a POSA to read Thomas (AMG1023) for the structure and sequence of the "eculizumab" antibody shown to block C5 cleavage and to safely and effectively treat PNH. (*See, e.g.*, AMG1004 at 553 (citing AMG1023 (Ref. No. 15)); AMG1047 at 2559 (citing AMG1023 (Ref. No. 9)); AMG1012 at 1234 (citing AMG1023 (Ref. No. 13)); AMG1005 ¶ [0052] (citing AMG1023); AMG1021 at 1018 (citing AMG1023 (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***" heavy chain constant region, which was selected because the IgG4 isotype was thought to avoid activating human complement. (AMG1023 at 1396, 1399.) Thomas reported data showing that the IgG4 humanized antibody had suitable affinity and specificity, and was as effective as the original mouse antibody (termed "murine 5G1.1" or "m5G1.1") in an *in vitro*

assay showing activity blocking C5 cleavage and preventing lysis of blood cells due to complement activity. (AMG1023 at 1396.)

From Thomas, a POSA as of March 15, 2007 would have understood that Alexion's development of "eculizumab" as a clinically successful antibody involved substantial work. Alexion (1) generated anti-human C5 antibodies in mice, (2) screened many different mouse ("murine") antibodies for their ability to block C5 cleavage, (3) cloned and purified a subset of antibodies that blocked C5, (4) isolated the most promising murine clone, (5) cloned and grafted the CDR regions – and any framework amino acids required for binding – from the murine antibody on to human heavy and light chain "framework" variable regions, (5) joined the "humanized" variable regions to human constant regions to construct complete antibodies, and (6) tested the full antibodies to determine if they maintained binding efficacy and specificity. (*See* AMG1023 at 1390-93.) Alexion then undertook extensive human testing to determine whether the resulting antibody – "eculizumab" – was safe and effective in treating patients with PNH. (AMG1004; AMG1047; AMG1012; AMG1005 ¶¶ [0081]-[0096].)

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

Today, but ***not*** prior to the March 15, 2007 priority date for the '880 patent, it is known that SOLIRIS® has the specific amino acid sequence recited in the

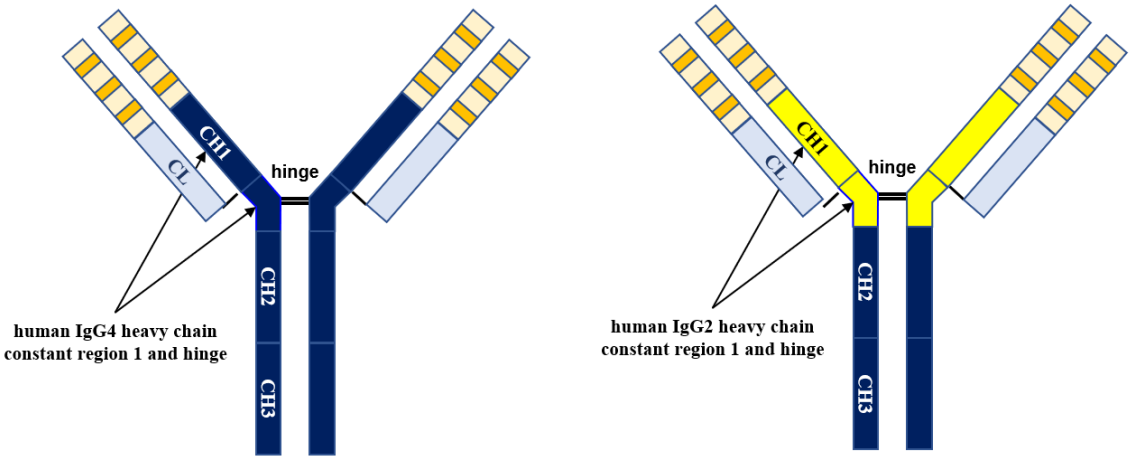
claims of the ’880 patent, namely, “a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.” A POSA prior to the ’880 patent, however, would not have reasonably expected that an antibody consisting of SEQ ID NOs: 2 and 4 would work to prevent C5 cleavage or would safely and effectively treat conditions such as PNH.

Today, but ***not*** prior to March 15, 2007, it is known that SOLIRIS® is a unique antibody that is ***very different*** from the humanized IgG4 antibody described in Thomas. As understood today, 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 – that was designed by scientists at Alexion and was thoroughly tested in human clinical trials. (AMG1033 at 1257-1258.) Notably, SOLIRIS® was the first FDA-approved product containing Alexion’s uniquely-engineered heavy chain constant 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 SOLIRIS® that is known today and claimed in the ’880 patent is shown below in comparison to the IgG4 isotype antibody described in Thomas, which the literature prior to March 15, 2007 would have taught a POSA was “eculizumab.” The figure depicts how, unlike the IgG4 antibody of Thomas,

the claimed antibody uses the CH1 and "hinge" regions of IgG2, thereby providing a very different antibody than that identified in the literature citing to Thomas.

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



E. Overview of the '880 Patent

The '880 patent issued on August 1, 2017 from U.S. App. No. 15/148,839, filed on May 6, 2016, and claims priority back to PCT/US2007/006606, filed on March 15, 2007. The patent has three claims:

> **1.** A pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody solution, wherein the antibody comprises a heavy chain consisting

> of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
>
> **2.** A pharmaceutical composition comprising an anti-C5 antibody, wherein the anti-C5 antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
>
> **3.** The pharmaceutical composition of **claim 2**, wherein the pharmaceutical composition is a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution.

(AMG1001 at 39:1-16.)

The ’880 patent claims recite the complete amino acid sequence for SOLIRIS®, which was not known prior to the March 15, 2007 priority date: the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001 at cols. 31-33, 35.) The ’880 patent also provides Phase III clinical data from the “TRIUMPH” study confirming that the claimed antibody is safe and effective for treating PNH, and identifying the safe and effective dosing regimen for that use. (AMG1001 at abstract, 19:41-28:38.)

The challenged ’880 patent claims therefore reflect the invention’s purpose: the development of a humanized monoclonal antibody, and pharmaceutical

compositions thereof, that can block cleavage of C5 and be used as a safe and effective therapy for patients with PNH.

F. Prosecution History of the ’880 Patent and Related Applications

In the course of patent prosecution leading to issuance of the ’880 patent, as well as prosecution of related U.S. Patent Nos. 9,725,504 (“the ’504 patent”) and 9,732,149 (“the ’149 patent”), the Examiner considered the same, or substantially the same, prior art that Amgen now asserts in its Petition. In doing so, the Examiner made findings undermining Amgen’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.” (AMG1016 at 762-763.) The Examiner also found that SOLIRIS® and its unique sequence was not “accessible to the public” as of March 15, 2007. (*Id*.)

For example, in finding the claims of the ’880 patent to be novel and nonobvious, the Examiner:

- Expressly discussed Amgen’s asserted references Hillmen 2004 (AMG1004), Evans (AMG1007), and Wang (AMG1028) as a basis for rejection, before ultimately finding the claims to be allowable over the art (*see, e.g.*, AMG1016 at 120-121, 179-180, 598-602, 719-724);

- Considered Amgen's asserted references Hill 2005 (AMG1047) and Bell (AMG1005), which Alexion submitted to the PTO (*see, e.g.*, AMG1016 at 155, 158);
- Considered U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Amgen's cited "Bowdish" application (AMG1006), disclosing the same information on which Amgen relies here (*see, e.g.*, AMG1016 at 154); and
- Considered the "Mueller II" article (AMG1031), which is cumulative of Amgen's asserted "Mueller" reference (AMG1008) because, as Amgen's declarant recognized, it "discloses the same antibodies" as Mueller. (*See, e.g.*, AMG1016 at 625; AMG1002 ¶¶ 109-110 & n.12.)

Accordingly, contrary to Amgen's allegations, Alexion did not "mislead" the Patent Office or fail to disclose references pertaining to Amgen's arguments here. (*See, e.g.*, Petition at 6, 24.) For example, Alexion submitted, and the Examiner reviewed and considered, a Bowdish patent (ALXN2016) and the Mueller II article (AMG1031) that were cumulative of the Bowdish (AMG1006) and Mueller (AMG1008) references in all respects pertinent to Amgen's Grounds.

Notably, during prosecution of the '880 patent and the related patents, the Examiner confirmed a central fact that Amgen ignores in its Grounds: that

Hillmen 2004, 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." (AMG1014 at 559, 623 (citing AMG1023); *see also* AMG1016 at 598 (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 '880 patent, which contains the uniquely-engineered heavy chain reflected in SEQ ID NO: 2. (AMG1014 at 586-87, 591 ¶¶ 3-5.)

Amgen's assertion that the Examiner solely "relied upon Thomas for a teaching of the claimed sequence" is thus mistaken. (*See* Petition at 9.) Rather, the Examiner was guided by ***Hillmen 2004*** (AMG1004), which expressly instructed a POSA to look to Thomas for the structure and sequence of "eculizumab." After Alexion explained how Thomas's IgG4 constant region is very different from the uniquely-engineered constant region of SEQ ID NO: 2, the Examiner ultimately agreed that the prior art did not disclose or suggest the specific antibody sequence recited in the '880 patent claims. (AMG1016 at 762; *see also* AMG1014 at 790.)

Amgen also ignores the Declaration of Dr. Laural Boone (AMG1016 at 733-740 ("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. (AMG1016 at 762-63.) 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." (AMG1016 at 762-63; AMG1016 at 737-740 ¶¶ 6-13.) While, as Dr. Boone explained, it is known ***today*** that SOLIRIS® as used in these studies had the claimed sequence of SEQ ID NOs: 2 and 4 (AMG1016 at 737, ¶ 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 the IgG4 structure of Thomas.

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 SOLIRIS® nor its complete sequence (including the uniquely engineered sequence of its heavy chain constant region) was in the public domain prior to March 15, 2007, and accordingly allowed the '880 patent to issue. (AMG1016 at 761-63.)

Institution of Amgen's Petition, based on the same or substantially same cumulative art that was considered by the Examiner during prosecution, should therefore be denied under 35 U.S.C. § 325(d). (*See infra* Section VI.)

III. AMGEN MISSTATES THE SCOPE AND CONTENT OF THE ART IN HINDSIGHT

In addressing 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, Amgen provides a description of "state of the art before March 15, 2007" that is unduly selective and that was strategically crafted based on Amgen's hindsight knowledge of the specific sequence for the SOLIRIS® antibody as claimed in the '880 patent. Amgen 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, Amgen 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. Amgen also disregards the art's extensive teachings regarding the complexity and unpredictability of designing monoclonal antibodies for human therapy.

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

Amgen 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" – the anti-C5 antibody shown in the art to safely and effectively treat PNH.

A review of the prior art regarding "eculizumab" (including Amgen'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 a humanized antibody with an IgG4 heavy chain constant region as described in Thomas (AMG1023). (*See infra* Table 1.) Yet Amgen 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 what Amgen knows today only in hindsight: that the SOLIRIS® antibody that was ***actually*** approved by the FDA for treatment of PNH has a uniquely-engineered constant region that is very different from the IgG4 isotype of Thomas.

Accordingly, Amgen 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. Amgen also does not dispute that "eculizumab" – including its sequence and structural details – was, as of March 15, 2007, a proprietary, unapproved development candidate that was unavailable to the public and that Alexion maintained in strict confidence beyond what was reported in the literature.

Because Amgen's obviousness Grounds, as well as its anticipation Grounds, are tainted with this fundamental misapprehension of what the art taught regarding "eculizumab" as of March 15, 2007, Amgen's Petition fails.

1. Amgen Improperly Ignores the Art's Teaching that "Eculizumab" Was Described by Thomas

The most glaring evidence of Amgen's hindsight bias is its failure to acknowledge that ***its own cited art*** – including 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." (*See infra* Table 1.) It is undisputed that Thomas taught an antibody with an ***IgG4*** constant region that is very different from the uniquely-engineered constant region reflected in the claimed sequence of the '880 patent.

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

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

Amgen Exhibit	Statement Identifying "Eculizumab" as the IgG4 Construct of Thomas (AMG1023)
Hillmen 2004 (AMG1004) 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. . . ."
Hill 2005 (AMG1047) 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."

Amgen Exhibit	Statement Identifying "Eculizumab" as the IgG4 Construct of Thomas (AMG1023)
Hillmen 2006 (AMG1012) 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."
Bell (AMG1005) 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 (AMG1021) at 1018	Cites ***Thomas***, Ref. No. [258884], for synthesis of "[h]umanized 5G1.1," also identified as "eculizumab."
Brekke (AMG1019) at 56	Cites Kaplan (AMG1021), Ref. No. 31, as describing "[e]culizumab" as "a humanized monoclonal antibody that prevents the cleavage of human complement component C5." In turn, Kaplan cites to ***Thomas***.

Amgen Exhibit	Statement Identifying "Eculizumab" as the IgG4 Construct of Thomas (AMG1023)
Pierangeli (AMG1020) at 2123	Cites to Hillmen 2004 (AMG1004), Ref. No. 18, as describing "eculizumab [that] has been shown to prevent C5 activation in humans and to have beneficial effects in patients with [PNH]." In turn, Hillmen 2004 cites to ***Thomas***.
Tacken (AMG1034) at 1279	Cites ***Thomas***, Ref. No. 19, as describing the antibody "h5G1.1-mAb (5G1.1, eculizumab; Alexion Pharmaceuticals)"

Notably, each of Amgen's six Grounds includes at least one reference teaching that the clinically safe and effective "eculizumab" antibody was the IgG4 antibody of Thomas. (*See* Hillmen 2004 (AMG1004) (Grounds 1 and 3); Hill 2005 (AMG1047) (Grounds 2 and 4); Bell (AMG1005) (Grounds 3-6).)

There is no excuse for Amgen's disregard of the art's consistent teaching as of March 15, 2007 that "eculizumab" had the structure and sequence of Thomas's IgG4 isotype antibody. For example, in citing Hill (AMG1047) for describing how "eculizumab" demonstrated long-term safety and sustained response against PNH, Amgen and its declarant Dr. Balthasar quote directly from the sentence that cites Thomas (Ref. No. 9): "Eculizumab is a humanized monoclonal antibody that

specifically targets the complement protein C5 and prevents its cleavage." (*Compare* Petition at 32 and AMG1002 ¶ 83 *with* AMG1047 at 2559, 2565.) Yet, Amgen ignores Hill's citation to Thomas entirely. The same is true for Hillmen (AMG1004), where Amgen and Dr. Balthasar quote directly from the paragraph that directs a POSA to Thomas (Ref. No. 15) for details regarding "eculizumab," but then ignore the reference to Thomas entirely. (*Compare* Petition at 25-26 and AMG1002 ¶ 74 *with* AMG1004 at 553, 559.)

Rather than acknowledge the art's consistent pointing to Thomas for details regarding the structure of "eculizumab," Amgen and Dr. Balthasar attempt to dismiss Thomas as immaterial. (*See, e.g.*, AMG1002 ¶ 49 ("[A] POSA would have known that t[he] antibody [of Thomas] was not eculizumab."); Petition at 14 n.9 ("A POSA would have readily distinguished [the Thomas antibody] from eculizumab.").) But Amgen's arguments regarding Thomas are hollow and tainted by circular logic and hindsight. In particular, Amgen assumes, without basis, that a POSA would have distinguished Thomas's antibody from "eculizumab," when the literature as of March 15, 2007 clearly and consistently taught that "eculizumab" ***was*** the humanized IgG4 antibody of Thomas. (*See supra* Table 1.)

While ***today*** SOLIRIS® (eculizumab) is known to have the non-naturally occurring, uniquely-engineered heavy chain constant region reflected in SEQ ID NO: 2 of the '880 patent, Amgen 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 – including publications from the named inventors – that described "eculizumab" by pointing to Thomas's IgG4 antibody. As discussed above, even the Examiner of the '880 patent and related patents concluded that Hillmen 2004 directed a POSA to look at Thomas for a detailed description of "eculizumab":

> Hillmen discloses (p. 553, 3rd¶) that eculizumab is a recombinant human antibody that binds to C5, ***and refers to reference number 15 (Thomas) as disclosing more information about eculizumab***.

(AMG1014 at 559; *infra* Section II.F; *see also* AMG1016 at 558.) Amgen cannot ignore Hillmen's teaching to a POSA as of March 15, 2007 that "eculizumab" was the IgG4 antibody of Thomas.

In addition to the many differences between Thomas's IgG4 antibody and the '880 patent's SEQ ID NO: 2, Thomas's antibody differs from the '880 patent's SEQ ID NO: 4 in the light chain variable region between CDR1 and CDR2. For this reason, too, the art citing to Thomas would have pointed a POSA away from the claimed sequence of the '880 patent. Specifically, SEQ ID NO: 4 has a glutamine ("Gln") at position 38, whereas Thomas has an arginine ("R") at the corresponding position. (*Compare* '880 patent at SEQ ID NO: 4, position 38 *with*

AMG1023 at 1396, Figure 4, position 38 (last amino acid in the top row).) This difference occurs in the "framework" region, which could influence antigen binding and affinity. (*See, e.g.*, ALXN2017 at 961-62.) A POSA would not have had any reason to deviate from Thomas's reported sequence, since the literature identified Thomas's antibody as "eculizumab" that was successful in clinical trials for treating PNH, and a POSA would have understood that altering the variable region sequence could change the antibody's binding properties and safety in humans.

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

None of Amgen'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 the IgG4 isotype structure described in Thomas. The errors in Amgen's arguments are compounded by Amgen's attempt to reconstruct the '880 patent's invention using hindsight knowledge of the claimed amino acid sequence – picking and choosing from documents that a POSA would never have even looked to for information regarding the complete structure of "eculizumab." (Petition at 13-18.) *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.").

Contrary to Amgen's assertions, a POSA as of March 15, 2007 would not have envisioned "eculizumab" to have the uniquely-engineered constant region reflected in SEQ ID NO: 2 of the '880 patent. Amgen suggests that "eculizumab" was somehow disclosed or claimed by the Evans patent (AMG1007) (*e.g.*, Petition 2-3, 8, 56, 60-61)[2] – but it is undisputed that Evans neither used the term "eculizumab," nor disclosed the heavy chain constant region or full sequence of the

[2] With respect to the Patent Term Extension ("PTE") applied to the Evans patent following approval of SOLIRIS® (AMG1009; AMG1010), the application makes clear that Evans's claims "read on" SOLIRIS® in a generic sense, with purely functional claims defined by binding properties (*e.g.*, Evans claim 1), or functional claims including the sequence for only the CDRs in the antibody variable region (*e.g.*, Evans claim 19). (AMG1009 at 4-7.) Nothing in the PTE application suggested that Evans taught the complete sequence recited in the '880 patent claims.

claimed antibody of the ’880 patent. (*e.g.*, Petition at 54, 60-61.) As Amgen 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.*, AMG1007 at 43:6-45:4; Petition at 61.) Further, Evans only describes antibody heavy chain 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. (AMG1007 at 45:24-33; Petition at 61.) Nothing in this paragraph, or elsewhere in Evans, suggests or discloses constructing the uniquely-engineered heavy chain constant region of the ’880 patent’s SEQ ID NO: 2; and a POSA as of March 15, 2007, understanding from the literature that the IgG4 isotype antibody of Thomas was clinically successful, would have had no reason to do so. Contrary to Amgen’s suggestions, Evans would not have led a POSA to make an antibody with the specific amino acid sequence described and claimed in the ’880 patent.

Bowdish (AMG1006) and Mueller (AMG1008) are even further afield from the problem addressed by the ’880 patent’s claimed invention – and would not have given a POSA as of March 15, 2007 any reason to doubt the art’s clear teaching that the clinically successful “eculizumab” antibody was the IgG4 construct described in Thomas (AMG1023). 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 ’880 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*. (AMG1006 ¶¶ [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 and has nothing to do with cleavage of C5. (AMG1006 ¶ [0192].) Amgen does not and cannot explain why a POSA seeking a safe and effective anti-C5 antibody composition for the treatment PNH would have looked to Bowdish, which addresses an entirely unrelated problem from that solved by the ’880 patent. *See, e.g.*, *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013).

Likewise, Mueller, and the associated article Mueller II (AMG1031), concerned an issue unrelated to the ’880 patent – developing antibodies to vascular cell adhesion molecules (“VCAM”) to block transplant rejection. (AMG1008 at 8:23-26, 37:22-36; AMG1031 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. (AMG1008 at 12:19-32; AMG1031 at 442-443.)

Amgen also cannot explain why a POSA as of March 15, 2007 would have turned to Bowdish or Mueller for a description of "eculizumab." Critically, neither Bowdish nor Mueller mention the term "eculizumab." Nonetheless, Amgen reveals its reliance on hindsight by repeatedly using the term "eculizumab" when describing the teachings of Bowdish and Mueller – even inserting the term "eculizumab" into quotes where it does not appear. (*See, e.g.*, Petition at 4-6, 14-16, 67.) There is no reason why a POSA as of March 15, 2007 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.

Amgen 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 5, 13, 15-16, 55-56, 66-67.) As Amgen 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 15 (citing AMG1007 at 9:65-10:20

& Figs. 18-19)), 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 60-61 (citing AMG1007 at 42:58-45:4)), as well as Thomas's humanized IgG4 construct that the literature as of March 15, 2007 described as "eculizumab" (Petition at 14 n.9 (citing AMG1023)). And even in its hindsight effort to connect the broad terms "5G1.1" or "h5G1.1" with "eculizumab," Amgen relies on documents that identified "eculizumab" as the IgG4 antibody of Thomas. (*See* Petition at 13 n.8 (citing AMG1019, AMG1020, AMG1021); *supra* at Table 1.) Thus, neither Bowdish's reference to using "5G1.1" as a scaffold for a TPO-mimetic peptide (AMG1006 ¶¶ [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.

Likewise, Mueller's reference to "h5G1.1 CO12 HuG2/G4 mAb" for use as an experimental isotype control antibody (AMG1008 at 9:6-9, 12:34-37) would not have taught a POSA about the structure of the "eculizumab" antibody 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 constant region ("h5G1.1 CO12 HuG4 mAb") as an isotype control (*see* AMG1008 at 11:36-12:4, Figures 11-13; *see also* AMG1031 at 444-445, Figure 3) – and Amgen does not

explain why a POSA reading Mueller would have singled out the "HuG2/G4" and assumed it to be 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 the IgG4 isotype of Thomas. (*See supra* 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 constant region of SEQ ID NO: 2 would have been safe for human use. While Amgen cites to statements in Mueller II that antibodies with an "IgG2/G4" hybrid constant region would not "likely be immunogenic" (Petition at 69 (citing AMG1031 at 448, 451)), a POSA would have understood those statements to be speculative and unstudied in human clinical trials. In contrast, a POSA as of March 15, 2007 would have understood the literature regarding clinical studies of "eculizumab" to indicate that Thomas's IgG4 antibody was safe when administered to humans. (*See supra* Section II.C.) Consistent with a POSA's understanding from the literature regarding "eculizumab," Thomas itself also predicted that the IgG4 antibody construct would avoid complement activation, and would otherwise be "minimally immunogenic in patients." (AMG1023 at 1399.) Nothing in Mueller or elsewhere in the art would have motivated a POSA to abandon the structure of the antibody

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

Amgen's arguments also fail because they are based on the erroneous assumption that a POSA as of March 15, 2007 would have understood "eculizumab" to contain "a hybrid IgG2/IgG4 constant region." (*See, e.g.*, Petition at 13-14, 55; AMG1002 ¶¶ 44, 47.) For this hindsight-based argument, Amgen relies on only two sources, neither of which are part of any of Amgen's six "Grounds": (1) an isolated statement taken out of context from the Tacken article (AMG1034) directed to a different field of endeavor; and (2) a non-prior art (*i.e.*, 2011) statement taken out of context from the file history of an unrelated patent application (AMG1049). But neither of these statements from non-analogous and non-prior art documents contradict the overwhelming teaching in the pertinent art as of March 15, 2007 that the "eculizumab" antibody known to prevent C5 cleavage and to safely and effectively treat PNH had the sequence of Thomas's humanized ***IgG4*** antibody. (*See supra* Section II.C and III.A.1.)

Amgen misreads Tacken, which does not involve the same field as the '880 patent, and would not have been reasonably pertinent to the particular problem addressed by the '880 patent. *See, e.g., Circuit Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1335 (Fed. Cir. 2015). Unlike the clinical literature discussed in Section II.C above, Tacken did not concern the study of "eculizumab" in binding C5, blocking

C5 cleavage or treating PNH, but rather involved the study of a different antibody (the "hD1" antibody) with a wholly different purpose: directing antigens to a dendritic cell receptor for purposes of developing improved vaccinations. (AMG1034 at 1278-79, 1283-84.)

Nothing in Tacken contradicted the consistent teaching of the prior art that "eculizumab" had an IgG4 constant region. Solely for purposes as an "isotype control antibody" for use in experiments involving dendritic cells, Tacken described an antibody "h5G1.1-mAb" that was altered to "contain[] the same IgG2/IgG4 constant region" as the "hD1" antibody directed to dendritic cells. (AMG1034 at 1279.) A POSA would ***not*** have understood this "isotype control antibody" to be the "eculizumab" antibody shown in the clinical literature to block C5 cleavage and safely and effectively treat PNH. Rather, consistent with the other teachings in the art, Tacken identifies "eculizamab" [sic] as the antibody described by ***Thomas*** (cited as Tacken Ref. No. 19). (AMG1034 at 1279, 1285.) The art following Tacken's publication further confirmed that understanding. For example, Hillmen 2006 (AMG1012), reporting on Alexion's Phase III clinical study for "eculizumab" in treating PNH, cited Thomas as describing "[e]culizumab (Soliris, Alexion Pharmaceuticals) . . . a humanized monoclonal antibody directed against the terminal complement protein C5." (AMG1012 at 1234, 1243 (citing Thomas (AMG1023), Ref. No. 13).)

Amgen's arguments regarding the non-prior art statements taken out of context from the file history of U.S. App. No. 11/127,438 ("the '438 application") – which is not related to the '880 patent at issue here – fare no better. (*See, e.g.*, Petition at 14 (citing AMG1049 at 838-39.) The statements Amgen cites were made in August 2011 – years after the March 15, 2007 priority date for the '880 patent. (AMG1049 at 855.) Amgen commits legal error by relying on these non-prior art statements made with hindsight knowledge of Alexion's inventions, rather than "look[ing] ***at the prior art*** [to] determine what it teaches to an ordinary artisan ***without the benefit of the invention*** . . . ."[3] *See Neptune Generics, LLC v. Eli Lilly & Co.*, IPR2016-00237, Paper 84 at 74-77 (Oct. 5, 2017), *aff'd*, 921 F.3d 1372 (Fed. Cir. 2019) (PTAB "declin[ing] to read the [prior art] in view of" the patent owner's non-prior art statements to the FDA).

Further, when read in context, the non-prior art statements that Amgen pulls from the '438 application file history cite ***nothing*** in the prior art contradicting the fact that, as of March 15, 2007, the art taught that the clinically successful "eculizumab" antibody had an IgG4 constant region as described in Thomas. (*See*

[3] Dr. Balthasar also uses improper hindsight by relying on a non-prior art (November 2007) Alexion article for his understanding of "eculizumab's heavy chain." (AMG1002 ¶ 56 (citing AMG1033).)

supra at Section II.C.) Rather, those non-prior art statements refer to Mueller II (AMG1031), which, as discussed above, would not have taught a POSA as of March 15, 2007 the unique structure and specific amino acid sequence reflected in the claims of the ’880 patent.

B. Amgen Ignores the Art Regarding the Complexity and Unpredictability of Designing Monoclonal Antibodies for Human Clinical Therapy as of March 15, 2007

A POSA as of March 15, 2007 would not have had any motivation to alter the specific structure or sequence of “eculizumab” as described in the art at that time, and would not have reasonably expected success in doing so. As discussed above, a POSA as of March 15, 2007 would have understood “eculizumab,” the antibody reported as preventing cleavage of C5 and safely and effectively treating patients with PNH, to be the IgG4 antibody described in Thomas. (*See supra* Section II.C.) Thomas predicted that its IgG4 antibody would be potent in preventing C5 cleavage and “minimally immunogenic in patients” (AMG1023 at 1399), and the published Phase II and Phase III clinical trials that referred to Thomas as describing “eculizumab” confirmed those predictions to a POSA. (*See supra* Section II.C.)

With that knowledge, a POSA as of March 15, 2007 would have had no reason to deviate from the structure of “eculizumab” that they understood to be 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 heavy chain constant region isotype of a known antibody, even if the variable region were left unchanged. Specifically, the art described how such "isotype switching" could affect critical properties including, among other things, antigen binding affinity and specificity. (*See, e.g.*, ALXN2011 at 2240, 2242 (showing that antibodies expressing the same variable regions but different heavy chain constant regions "bind [antigen] with ***significant differences in affinity***"); ALXN2008 at 169, 171 Fig. 1 (noting that despite having identical variable regions, the constant region structures of four isotype subclasses tested "clearly influenced functional antibody affinity" and "[t]he exact mechanism for this phenomenon remains obscure"); ALXN2013 at 1379, 1380-81, 1384-86 (presenting "unexpected" results indicating that "isotype switching may lead to loss of recognition of the original [antigen] as

well as the recognition of new epitopes"); ALXN2010 at 3 (review summarizing studies from prior to 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 "CH1" and "hinge" portions of the heavy chain constant region 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 constant region, such as a hybrid sequence constructed from portions of the IgG2 and IgG4 heavy chains, 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 use as human therapies, Amgen 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 the IgG4 isotype antibody of Thomas – would have been motivated to create a very different antibody with potentially very different clinical properties

by instead using the uniquely-engineered heavy chain constant region reflected in SEQ ID NO: 2 of the '880 patent. Nor can Amgen explain how a POSA would have reasonably expected to succeed in using an antibody that deviated from the structure of "eculizumab" that was 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 constant region of SOLIRIS® (*see, e.g.*, AMG1029 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 heavy chain constant region.

C. Amgen Fails to Show that All Elements of the Claimed Pharmaceutical Compositions of the '880 Patent Were Disclosed in the Prior Art

Amgen also cannot show any teaching in the prior art of the additional elements defining the pharmaceutical compositions of the '880 patent claims. For example, neither Bell nor Wang, cited in Amgen's Grounds 3-6, discloses the elements of a "300 mg single-use dosage form" or "30 ml of a 10 mg/ml antibody solution." Bell merely described administration of 600 and 900 mg doses of "eculizumab" without identifying the dosage unit or concentration of the administered pharmaceutical composition. (AMG1005 ¶¶ [0082], [0091].) And

Wang described a broad range of possible concentrations (1-200 mg/ml) for formulating various antibodies (AMG1028 ¶ [0067]), without teaching the specific 10 mg/ml antibody concentration of the claimed antibody of the ’880 patent. Amgen cannot explain how a POSA without hindsight would have arrived at the specific dosage unit, concentration and volume recited in claims 1 and 3 of the ’880 patent.

IV. PERSON OF ORDINARY SKILL IN THE ART OF THE ’880 PATENT

Amgen contends that a POSA would have had “an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with ***at least two years of experience in the field***.” (Petition at 21-22.) Amgen does not dispute that the ’880 patent concerns pharmaceutical compositions of an anti-C5 antibody, defined by its specific amino acid sequence, that are suitable for treatment of patients with PNH. (Petition at 1.)

Alexion does not dispute Amgen’s POSA definition, 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, Amgen cannot prove unpatentability of the challenged claims of the ’880 patent under any of its six fatally flawed Grounds.

V. AMGEN'S PETITION FAILS TO SHOW UNPATENTABILITY OF ANY CHALLENGED CLAIM OF THE '880 PATENT

A. Amgen's Grounds 1 and 2 Fail Because Amgen Cannot Show that Claim 2 Was Anticipated by Hillmen 2004 or Hill 2005

Amgen's Grounds 1 and 2 contend that claim 2 (but not claims 1 or 3) of the '880 patent was anticipated by the clinical trial publications Hillmen 2004 (AMG1004) or Hill 2005 (AMG1047), respectively. Since both Grounds raise essentially identical issues, and both Grounds fail for essentially the same reasons, Alexion addresses both Grounds together here.

1. Hillmen 2004 and Hill 2005 Do Not Disclose "a Heavy Chain Consisting of SEQ ID NO: 2"

Amgen's Grounds 1 and 2 fail because neither Hillmen nor Hill expressly or inherently disclosed all the elements recited in claim 2 of the '880 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.").

Significantly, both Hillmen and Hill failed to disclose at least the element of "a heavy chain consisting of SEQ ID NO: 2." While both Hillmen and Hill describe administering "eculizumab" for treating PNH, ***nothing*** in Hillmen or Hill taught the non-naturally occurring, uniquely-engineered heavy chain constant region of SOLIRIS® that is reflected in the '880 patent's "SEQ ID NO: 2." (*See supra* Section III.A.1.) Rather, both Hillmen and Hill referenced Thomas

(AMG1023) to further describe "eculizumab," which in turn taught an antibody with an "***IgG4***" heavy chain constant region having a very different amino acid sequence from the heavy chain constant region reflected in the '880 patent's "SEQ ID NO: 2." (*See supra* Section II.C.)

Accordingly, neither Hillmen nor Hill, including their references to "eculizumab," disclosed each and every element of claim 2 of the '880 patent. Nor could Hillmen or Hill have enabled a POSA to make and use the specific antibody recited in claim 2 without undue experimentation, because both Hillmen and Hill guided a POSA as of March 15, 2007 to make and use a very different antibody – the ***IgG4*** isotype antibody of Thomas. *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").

Amgen further concedes that neither Hillmen nor Hill disclosed or enabled the invention of claim 2, because Amgen'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, and Mueller. (*See* Petition at 30, 34-35.) Amgen's "enablement" arguments appear to be a restatement of the obviousness arguments that Amgen asserts under Grounds 5 and 6, which Amgen 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, Amgen has failed to show that a POSA provided with Hillmen or Hill and the Evans, Bowdish or Mueller references as of March 15, 2007 would have been led to the '880 patent's claimed amino acid sequence without undue experimentation, when Hillmen, Hill, and the many other references listed in Table 1 taught a POSA that "eculizumab" was Thomas's IgG4 antibody construct. (*See supra* Section II.C and III.A.1.)

2. Neither Hillmen 2004 nor Hill 2005 Inherently Disclosed the Unique, Non-Public Amino Acid Sequence of SOLIRIS® Recited in Claim 2 of the '880 Patent

Acknowledging that Hillmen and Hill fail to expressly disclose the amino acid sequence recited in claim 2 of the '880 patent, including the uniquely-engineered heavy chain constant region in "SEQ ID NO: 2," Amgen 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 26, 31-34.) As explained below, however, Amgen'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, Amgen alleges inherent anticipation of claim 2 on the grounds that ***today*** – years after the '880 patent's March 15, 2007 priority date – it is known that the clinical studies underlying the Hillmen and Hill publications ***actually*** used an antibody with a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4. (*See, e.g.*, Petition at 26 (citing Boone Declaration, AMG1014 at 763-770).) But Amgen is mistaken on the law. The mere naming of an investigational product (*e.g.*, "eculizumab") in a prior art publication does ***not*** inherently anticipate later-filed patent claims detailing the specific structure or composition of that product (*i.e.*, SEQ ID NOs: 2 and 4), if a POSA could not have ***necessarily*** determined the later claimed structure/composition from the information publicly available as of the priority date. *See, e.g., Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-83 (Fed. Cir. 2018). Likewise, post-filing information showing that the later-claimed antibody sequence was actually used in the studies underlying prior art clinical publications is insufficient to give rise to inherent anticipation, when those prior art publications would have guided a POSA to a different, unclaimed antibody sequence. *See, e.g.*, *id.*; *Bayer CropScience LP v. Syngenta Ltd.*, IPR2017-01332, Paper 15 at 3-6 (Apr. 2, 2018).

Accordingly, even if it is known today that the "eculizumab" antibody used in the clinical studies underlying the Hillmen and Hill publications was in fact the antibody recited in claim 2, Amgen has not shown inherent anticipation of that

claim. That is because Amgen fails to show that a POSA as of March 15, 2007 reading Hillmen or Hill 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 Hillmen or Hill as of that date would have envisioned that the antibody "eculizumab" was a very different antibody than what the '880 patent claims, having Thomas's "IgG4" heavy chain constant region rather than the unique, non-naturally occurring constant region reflected in "SEQ ID NO: 2." (*See supra* Section II.C.) 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 amino acid sequence of the antibody clinically tested in Hillmen and Hill. Rather, as discussed in the Boone Declaration during prosecution of the '880 patent (AMG1016 at 737-740), Alexion kept the amino acid 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 supra* Section II.F.)

Amgen incorrectly relies on *In re Crish*, 393 F.3d 1253, 1256 (Fed. Cir. 2004), which is distinguishable on the facts here. *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 Hillmen and Hill, 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 Hillmen and Hill 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 Hillmen and Hill 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 2 of the ’880 patent. (*See supra* Section II.F.) Accordingly, *In re Crish* does not merit a finding that either Hillmen or Hill inherently anticipate claim 2 of the ’880 patent.

As Amgen cannot show the presence of all of the elements of claim 2 in Hillmen or Hill, Grounds 1 and 2 fail the standard for institution.

B. Amgen’s Grounds 3 and 4 Fail Because Amgen Cannot Show that Claims 1 and 3 Would Have Been Obvious Over Hillmen 2004 or Hill 2005 in Combination with Bell and Wang

Amgen’s Grounds 3 and 4 contend that claims 1 and 3 (but not claim 2) of the ’880 patent would have been rendered obvious by the clinical trial publications Hillmen 2004 or Hill 2005, respectively, in combination with the Bell (AMG1005) and Wang (AMG1028) references. As Grounds 3 and 4 raise essentially identical issues and both Grounds fail for essentially the same reasons, we address both Grounds together here.

Amgen’s Grounds 3 and 4 fail, because, among other things, Amgen cannot show that each element of the claimed invention was known or obvious in view of in the prior art. *See, e.g., ArcelorMittal France v. AK Steel Corp.*, 700 F.3d 1314, 1323 (Fed. Cir. 2012); *see also* 37 C.F.R. § 42.104(b)(4) (a petition for *inter partes* review of a patent on obviousness grounds “must specify where each element of the claim is found in the prior art patents or printed publications relied upon”).

In particular, Amgen's Grounds 3 and 4 rely upon Hillmen or Hill, respectively, as the sole prior art allegedly disclosing the claimed element of an antibody comprising "a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4" in claims 1 and 3 of the '880 patent. (*See* Petition at 36, 44.) But Amgen is severely mistaken, and its Grounds 3 and 4 should fail for that matter alone. As discussed in Section V.A above, neither Hillmen nor Hill disclosed the claimed antibody sequence either expressly or inherently. To the contrary, as discussed above, a POSA as of March 15, 2007 reading Hillmen or Hill would have envisioned that the "eculizumab" antibody shown in those studies to be safe and effective for treating PNH was the ***IgG4*** isotype antibody described in Thomas. Accordingly, Hillmen and Hill would have both ***taught away*** from the claimed compositions of the '880 patent, because they would have led a POSA "in a direction divergent from the path that was taken by the ['880 patent]" – *i.e.*, towards the IgG4 antibody of Thomas, and away from the very different, uniquely-engineered antibody claimed in the '880 patent. *See Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017).

The Bell (AMG1005) and Wang (AMG1028) references that Amgen combines with Hillmen or Hill in Grounds 3 and 4 do not otherwise teach the unique sequence recited in claims 1 and 3 of the '880 patent. Wang (AMG1028) was silent on the sequence for "eculizumab." And Bell, like Hillmen and Hill,

would have reinforced a POSA's understanding as of March 15, 2007 that "eculizumab" was the IgG4 isotype antibody of Thomas, because Bell cited Thomas as describing "[m]ethods for the preparation of h5G1.1-mAb . . . under the tradename eculizumab"[4] (AMG1005 ¶ [0052]), and described positive Phase II clinical results for "eculizumab" in PNH patients (AMG1005 ¶¶ [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 '880 patent.

Given the consistent teaching as of March 15, 2007 that "eculizumab" was the IgG4 antibody of Thomas, Amgen's Grounds 3 and 4 provide no reason why a POSA without hindsight would have found it obvious to use the very different, uniquely-engineered antibody as recited in claims 1 and 3 of the '880 patent, which was not described as having been tested for activity, safety or efficacy in any of the art alleged in Amgen's Grounds 3 and 4. (*See supra* Section II.C.) Nor would a

[4] While paragraph [0052] of Bell also cited Evans for the disclosure of antibody fragments, a POSA would have understood that Bell's statements regarding the complete antibody "eculizumab" must refer to Thomas, not Evans, because Evans provided only incomplete antibody sequences without a heavy chain constant region. (*See, e.g.*, AMG1007 at 43:6-14, 43:62-45:4.)

POSA have reasonably expected success in using such an altered antibody, given the unpredictable impact of even small amino acid changes on therapeutic antibody efficacy and safety. (*See supra* Section III.B.)

Further, as discussed in Section III.C above, none of Amgen's cited prior art, including Bell and Wang, disclosed the elements of a "300 mg single-use dosage form" or "30 ml of a 10 mg/ml antibody solution." Amgen concedes that Bell does not disclose a "300 mg single-use dosage form." (*See* Petition at 39-41.) Likewise, Amgen relies on Wang for the "10 mg/ml" concentration of claims 1 and 3, but concedes that Wang did not disclose any 10 mg/ml "eculizumab" composition. Amgen also fails to explain why it focuses on the exemplary "1-30 mg/ml" range recited in Wang, when Wang also describes exemplary ranges of 1-200 mg/ml and 40-200 mg/ml. (AMG1028 ¶ [0067], Figure 10.) Nor can Amgen explain how a POSA could have been guided by FDA-approved formulations of unrelated antibodies in concentrations ranging from 0.5-100 mg/ml to specifically select a 10 mg/ml concentration for the unique claimed antibody of the '880 patent. (*See* Petition at 42 (citing AMG1029).)

As Amgen cannot show obviousness of claims 1 or 3 of the '880 patent over Hillmen or Hill in combination with Bell and Wang, Grounds 3 and 4 fail the standard for institution.

C. Amgen's Ground 5 Fails Because Amgen Cannot Show that Claims 1-3 Would Have Been Obvious Over the Combination of Bowdish, Evans, Bell and Wang

Amgen's Ground 5 contends that claims 1-3 would have been obvious over a combination of Bowdish, Evans, Bell, and Wang. Amgen asserts that Bowdish and Evans would have led a POSA to the uniquely-engineered, non-naturally occurring antibody sequence recited in claims 1-3, and that the remaining claim elements would have been taught by Bell and Wang. (Petition at 46-58.)

Amgen's Ground 5 fails because Amgen cannot show how, without the benefit of hindsight, a POSA would have been motivated to select and combine Bowdish, Evans, Bell, and Wang to obtain the claimed invention, or how they could have reasonably expected to succeed in doing so.

Amgen's Ground 5 relies on impermissible hindsight bias, which the Supreme Court and the Federal Circuit have repeatedly warned against in evaluating obviousness. *See, e.g.*, *Graham*, 383 U.S. at 36; *Monarch Knitting Mach.*, 139 F.3d at 881 ("Defining the problem in terms of its solution reveals improper hindsight in the selection of prior art relevant to obviousness."); *Zoltek Corp. v. U.S.*, 815 F.3d 1302, 1313 (Fed. Cir. 2000) (warning against "the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher"). Here, Amgen uses its present-day knowledge of the SOLIRIS® antibody claimed in the '880 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, Amgen uses hindsight to ignore 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, Amgen's Ground 5 must fail.

Amgen cannot explain why a POSA seeking to develop an anti-C5 antibody composition for treating PNH, without hindsight, would 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 '880 patent, because it pertained to a wholly unrelated problem: using antibodies and fragments thereof solely as inert "scaffolds" for peptides (*e.g.*, TPO) so that those peptides could bind to their respective receptors (*e.g.*, the TPO receptor). *See, e.g.*, *Circuit Check*, 795 F.3d at 1335 ("[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 '880 patent. *Circuit Check*, 795 F.3d at 1335.

Further, there is no basis for Amgen'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 Amgen's assertions to the contrary further confirm its reliance on impermissible hindsight. (*See supra* Section III.A.2.) Bowdish only refers to its TPO-mimetic scaffold as "5G1.1" (AMG1006 ¶ [0191]) – a broad term that a POSA as of March 15, 2007 understood to encompass a wide variety of possible murine and humanized antibodies and fragments, and that was in no way limited to "eculizumab." (*See supra* Section III.A.2.) Evans, in turn, described only various variable region fragments of anti-C5 antibodies, and did not describe the heavy chain constant region of "eculizumab" or any other complete humanized anti-C5 antibody. (*See supra* Section III.A.2.) A POSA without hindsight would have had ***no reason*** to believe that combining Bowdish's TPO-mimetic construct with a sequence from Evans would lead to "eculizumab."

Amgen 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 supra* Table 1.) Amgen 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. *Millennium Pharm.*, 862 F.3d at 1366.

Even if Bowdish and Evans were combined as per Amgen's hindsight-driven theory, a POSA would not have reasonably expected the resulting compound to work in a pharmaceutical composition for 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 intended for human administration. (*See supra*

Section II.B.) A POSA would not have reasonably predicted the activity, safety or efficacy of the antibody that Amgen 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 *in vitro* and long-term clinical 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.

Amgen also cannot show how the other elements of claims 1 and 3 of the '880 patent, including a "300 mg single-use dosage form" or "30 ml of a 10 mg/ml antibody solution," would have been obvious to a POSA without hindsight. As with Grounds 3 and 4, Amgen relies on Bell and Wang for these elements, and Amgen's arguments alleging these elements are obvious fail for the same reasons explained above with respect to Grounds 3 and 4. (*See supra* Section V.B.)

As Amgen cannot show obviousness of claims 1-3 of the '880 patent over Bowdish, Evans, Bell and Wang, Ground 5 fails the standard for institution.

D. Amgen's Ground 6 Fails Because Amgen Cannot Show that Claims 1-3 Would Have Been Obvious Over the Combination of Mueller, Evans, Bell and Wang

Ground 6 fails for all the reasons Ground 5 fails. In Ground 6, Amgen replaces Bowdish (Ground 5) with Mueller. As with Ground 5, Amgen uses improper hindsight analysis, by reconstructing the claimed invention of the '880

patent from bits and pieces of sequences in Mueller and Evans, while ignoring the art that consistently taught away from such a combination.

A POSA as of March 15, 2007 considering the problem addressed by the '880 patent – designing anti-C5 antibody compositions to prevent cleavage of C5 and to treat PNH – would have had no reason to look at Mueller, which had nothing to do with that problem. *See, e.g.*, *Broadcom*, 732 F.3d at 1334. Instead, Mueller studied antibodies to the porcine VCAM protein, for treating or diagnosing human rejection of transplanted animal tissue. (AMG1008 at 37:22-36; AMG1031 at 441-443.) Mueller did not include any experiments or data on C5 binding, blocking C5 cleavage, or treating PNH. Insofar as Mueller described "h5G1.1" antibodies, with either IgG4 or "IgG2/G4" heavy chain constant regions, these were exclusively used as "isotype control" antibodies in studies measuring the activity of the anti-VCAM antibodies. (AMG1008 at 12:27-30; AMG1031 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.

Nor can Amgen 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 the ***IgG4*** humanized antibody of Thomas. (*See supra* Section III.A.1.) A POSA would have had no reason to deviate from what they understood to be the structure and sequence of "eculizumab," and instead make an antibody with a different sequence that a POSA would not have reasonably expected to still block C5 cleavage or be safe or effective for human administration to treat PNH. 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 constant region described in Mueller, which only featured *in vitro* experiments.

Amgen also cannot show how the other elements of claims 1 and 3 of the '880 patent, including a "300 mg single-use dosage form" or "30 ml of a 10 mg/ml antibody solution," would have been obvious to a POSA without the benefit of hindsight. As with Grounds 3-5, Amgen relies on Bell and Wang for these elements, and Amgen's arguments regarding the alleged obviousness of these elements fail for the same reasons explained above with respect to Grounds 3-5. (*See supra* Section V.B-C.)

As Amgen cannot show obviousness of claims 1-3 of the '880 patent over Mueller, Evans, Bell and Wang, Ground 6 fails the standard for institution.

E. The Objective Indicia of Nonobviousness Support Validity

Objective indicia of nonobviousness, including commercial success, long-felt but unmet need, and industry praise, further support the validity of the '880 patent claims. *See, e.g., LEO Pharm. Prods., Ltd. v. Rea,* 726 F.3d 1346, 1358 (Fed. Cir. 2013).

SOLIRIS®, the commercial embodiment of the '880 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® have exceeded $1 billion over the past three years 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 '880 patent, which claims pharmaceutical compositions of the uniquely-engineered, non-naturally occurring antibody responsible for the drug's clinical (and therefore commercial) success as a treatment for PNH, as well as the complement-mediated hemolytic condition aHUS. *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.)

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

Amgen's Petition should also be denied institution under 35 U.S.C. §§ 325(d) and 314(a), because Amgen's Grounds rely on the "same or substantially the same prior art or arguments" previously presented to the PTO. *See Cultec, Inc. v. Stormtech LLC*, IPR2017-00777, Paper 7 at 13 (Aug. 22, 2017) (informative); *Becton Dickinson v. Braun*, IPR2017-01586, Paper 8 at 16-18 (Dec. 15, 2017) (informative). Amgen has not shown error in the Examiner's evaluation of the art recycled in its Petition and Dr. Balthasar's declaration to merit a "re-do" before the Board.

During prosecution of the '880 patent and the related '504 and '149 patents, the Examiner extensively considered the same art and arguments that Amgen rehashes in its Grounds 1-4. With respect to Grounds 1 and 3, the Examiner

considered and rejected the argument that the claimed antibody sequence was disclosed by Hillmen (AMG1004), after Alexion explained how Hillmen pointed a POSA to the very different IgG4 antibody of Thomas (AMG1023) for the structure of "eculizumab." (*See supra* Section II.F.) Amgen's Grounds 2 and 4, relying on Hill (AMG1047) in place of Hillmen, fail for the same reason: Hill pointed a POSA to Thomas for the structure of "eculizumab." (*See supra* Sections V.A-B.) The Examiner's ultimate conclusion that none of the art (including Hillmen) taught the claimed antibody sequence is fatal to Amgen's Grounds 1-4.

The Examiner of the '880 patent also thoroughly considered Evans (Grounds 5-6) and Wang (Grounds 3-6), and reviewed other references pertaining directly to Amgen's Grounds, including Bell (AMG1005) (Grounds 3-6); U.S. Patent No. 7,482,435 (ALXN2016), which is cumulative of Bowdish (AMG1006) (Ground 5); and Mueller II (AMG1031), which is cumulative of Mueller (AMG1008) (Ground 6). After having reviewed all of those references, the Examiner concluded that nothing in the art taught or suggested an anti-C5 antibody with the specific sequence recited in claims 1-3 of the '880 patent. (*See supra* Section II.F.)

Accordingly, Amgen's Petition should be denied under 35 U.S.C. § 325(d). Alternatively, if the Board finds that fewer than all six Grounds meet the standard for § 325(d), institution of Amgen's Petition should still be denied in full, because institution on all six Grounds "would not be an efficient use of the Board's time

and resources." *See Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Paper 7 at 41-43 (Jan. 24, 2019) (informative) (citing 35 U.S.C. § 314(a)).

VII. CONCLUSION

For the reasons described herein, Amgen fails to show that any challenged claim of the '880 patent is unpatentable. Alexion respectfully submits that the Board should deny Amgen'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 2005-2021** were served via electronic mail June 6, 2019, in their entirety on the following:

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CERTIFICATION OF WORD COUNT

The undersigned hereby certifies that the portions of the above-captioned **PATENT OWNER'S PRELIMINARY RESPONSE** specified in 37 C.F.R. § 42.24 has 13,956 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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