

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2023-00998
Patent: 9,718,880

PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY

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EXHIBIT LIST¹

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

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

2011	Pritsch <i>et al.</i> , Can Immunoglobulin CH1 Constant Region Domain Modulate Antigen Binding Affinity of Antibodies?, J. CLIN. INVEST., 98(10): 2235-43 (1996)
2012	Pritsch <i>et al.</i> , Can Isotype Switch Modulate Antigen-Binding Affinity and Influence Clonal Selection?, EUR. J. IMMUNOL., 30: 3387-95 (2000)
2013	McLean <i>et al.</i> , Isotype Can Affect the Fine Specificity of an Antibody for a Polysaccharide Antigen, J. OF IMMUNOLOGY, 169: 1379-86 (2002)
2014	Greenspan <i>et al.</i> , Complementarity, Specificity and the Nature of Epitopes and Paratopes in Multivalent Interactions, IMMUNOL. TODAY, 16(5): 226-30 (1995)
2015	Radbruch, <i>et al.</i> , Drastic Change in Idiotypic but Not Antigen-Binding Specificity of an Antibody by a Single Amino-Acid Substitution, NATURE, 315(6): 506-508 (1985)
2016	U.S. Patent No. 7,482,435, issued to Bowdish <i>et al.</i>
2017	Hawkins <i>et al.</i> , The Contribution of Contact and Non-contact Residues of Antibody in the Affinity of Biding to Antigen: The Interaction of Mutant D1.3 Antibodies with Lysozyme, J. MOL. BIO., 234: 958-964 (1993)
2018	Hawkins <i>et al.</i> , The Contribution of Contact and Non-contact Residues of Antibody in the Affinity of Biding to Antigen: The Interaction of Mutant D1.3 Antibodies with Lysozyme, J. MOL. BIO., 234: 958-964 (1993)
2019	Ricklin & Lambris, Complement-Targeted Therapeutics, NATURE BIOTECHNOLOGY, 25(11); 1265-1275 (2007)
2020	Alexion Press Release, Alexion's Soliris® Receives 2008 Prix Galien USA Award for Best Biotechnology Product, September 25, 2008, available at https://news.alexion.com/press-release/company-news/alexions-soliris-receives-2008-prix-galien-usa-award-best-biotechnology-p (last visited May 15, 2019)

2021	BusinessWire, Alexion's Soliris® Receives 2009 Prix Galien France for Most Innovative Drug for Rare Disease, June 10, 2009, available at https://www.businesswire.com/news/home/20090610005826/en/Alexions-Soliris®-Receives-2009-Prix-Galien-France (last visited May 15, 2019)
2022	Declaration of Arturo Casadevall, M.D., Ph.D. in IPR2019-00740
2023	Curriculum Vitae of Arturo Casadevall, M.D., Ph.D. in IPR2019-00740
2024	Declaration of Bernhardt L. Trout, Ph.D. in IPR2019-00740
2025	Curriculum Vitae of Bernhardt L. Trout, Ph.D. in IPR2019-00740
2026	Declaration of Michel C. Nussenzweig, M.D., Ph.D.
2027	<i>Intentionally left blank/Reserved</i>
2028	Hill, et al., Erythropoietin treatment during complement inhibition with eculizumab in a patient with paroxysmal nocturnal hemoglobinuria, THE HEMATOLOGY JOURNAL, 31-33, 2007
2029	Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, U.S. Dept. of Health and Human Services, Food and Drug Admin., 1997
2030	3/16/2007 FDA Approves Alexion's Soliris™ for all Patients with PNH
2031	Janeway, et al., Immunobiology, The Immune System in Health and Disease, Appendix I: Immunologists' Toolbox, 6th ed. 2005
2032	<i>Intentionally left blank/Reserved</i>

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2034	Hwang, et al., Immunogenicity of engineered antibodies, SCIENCE DIRECT, 17 Jan. 2005
2035	Shepherd, et al., Monoclonal Antibodies, Oxford University Press, pp. 58-5 (Appendix) 2000
2036	Lo, Benny K., Antibody Engineering Methods and Protocols, METHODS IN MOLECULAR BIOLOGY, Vol. 248 2004
2037	Welt, et al., Phase I Study of Anticolon Cancer Humanized Antibody A33, CLINICAL CANCER RESEARCH, 2003
2038	Haller, et al., Safety Issues Specific to Clinical Development of Protein Therapeutics, NATURE PUBLISHING GROUP, 2008
2039	Torres, et al., Exchanging Murine and Human Immunoglobulin Constant Chains Affects the Kinetics and Thermodynamics of Antigen Binding and Chimeric Antibody Autoreactivity, PLOS ONE, 2007
2040	Torres, et al., Variable-Region-Identical Antibodies Different in Isotype Demonstrate Differences in Fine Specificity and Idiotype, JOURNAL OF IMMUNOLOGY, 2005
2041	<i>Intentionally left blank/Reserved</i>
2042	Mathieu, Barbara G., Clinical Testing of Biologically Derived Therapeutics, Biologics Development: A Regulatory Overview, 3d ed., 2004
2043	Andersen, et al., Production technologies for monoclonal antibodies and their fragments, SCIENCE DIRECT, 2004
2044	Chadd, et al., Therapeutic antibody expression technology, 2001
2045	2007 USP Dictionary of USAN and International Drug Names
2046	Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances, 1997

2047	McClean, et al., A point mutation in the CH3 domain of human IgG3 inhibits antibody secretion without affecting antigen specificity, MOLECULAR IMMUNOLOGY, 2005
2048	<i>Intentionally left blank/Reserved</i>
2049	HemOnc Today, Eculizumab's triumph over PNH, https://www.healio.com/hematology-oncology/news/print/hemonc-today/%7B01f97d7b-36b4-4462-aab4-02918370caa1%7D/eculizumabs-triumph-over-pnh (Aug. 25, 2008)
2050	Fatimah Al-Ani et al., "Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations, Ther. Clin. Risk Manag., 12:1161-1170 (2016)
2051	Foote, Jefferson and Winter, Greg, "Antibody Framework Residues Affecting the Conformation of the Hypervariable Loops," J. Mol. Biol., 224:487-449 (1992)
2052	Xiang, Jim et al., Framework Residues 71 and 93 of the Chimeric B72.3 Antibody are Major Determinants of the Conformation of Heavy-chain Hypervariable Loops," J. Mol. Biol. 253:385-390 (1995)
2053	June 2019 Soliris [®] Label
2054	Alexion Press Release, "Alexion Pharmaceuticals Submits Biologics License Application for Soliris [™] (eculizumab)," (Sept. 20, 2006)
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2075	GenScript, "Final Report- Antibody Full Length Sequencing of Hybridoma 5G1.1 T175," Order Number: U856UEK140-1 (Nov. 15, 2019)

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2079	Chang, Byeong S. and Hershenson, Susan, "Practical Approaches to Protein Formulation Development," Pharmaceutical Biotechnology Vol. 13, 1-25 (2002)
2080	Wang, Wei, "Instability, stabilization, and formulation of liquid protein pharmaceuticals," International Journal of Pharmaceutics, 185:129-188 (April 28, 1999)
2081	Hermeling, S. et al., "Structure-Immunogenicity Relationships of Therapeutic Proteins, " Pharmaceutical Research, 12:6, 897-903 (June 2004)
2082	Frokjaer, Sven and Otzen, Daniel E., "Protein Drug Stability: A Formulation Challenge," Nature Reviews, Drug Discovery, 4:298-306 (April 2005)
2083	Rosenberg, Amy S., "Effects of Protein Aggregates: An Immunologic Perspective," AAPS Journal 8, Article 59, pp. E501-E507 (Aug. 4, 2006)
2084	ICH Topic Q5C, "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products," European Medicines Agency (July 1996)
2085	U.S. Depart of Health and Human Services, FDA, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products," ICH Rev. 2 (Nov. 2003)
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2089	Generium Pharmaceutical, “Elizaria” Product (2019)
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2091	Harlow and Lane, Chapter 15: Antibody Molecules, in <i>Antibodies, A Laboratory Manual</i> , 622-25 (1988)
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2100	Rother, R., <i>et al.</i> , "Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria," <i>Nature Biotechnology</i> 25: 1256-1264 (2007)
2101	<i>Intentionally left blank</i>
2102	Prosecution History for U.S. Patent No. 10,590,189 B2, submitted by Petitioner Samsung BioEpis Co., Ltd. in IPR2023-01069 as EX1002
2103	Prosecution History for U.S. Patent No. 9,725,504 B2, submitted by Petitioner Samsung BioEpis Co., Ltd. in IPR2023-00999 as EX1002
2104	Deposition Transcript of Jeffrey V. Ravetch, M.D. (Feb. 23, 2024)
2105	Declaration of Arturo Casadevall, M.D., Ph.D., 2024
2106	Deposition Transcript of Cindy Ippoliti, Pharm.D. (Feb. 20, 2024)

2107	Declaration of Bernhardt L. Trout, Ph.D., 2024
2108	Deposition Transcript of Jeffrey V. Ravetch, M.D., Ph.D. (July 16, 2024)

I. INTRODUCTION

Samsung still fails to prove the unpatentability of claims 1-3 of U.S. Patent No. 9,718,880 (“the ’880 patent”). In its Reply, Samsung doubles down on its hindsight obviousness arguments, continuing to use Alexion’s innovative IgG2/IgG4 claimed sequence as a road map to reverse-engineer eculizumab. Samsung’s arguments based on Bowdish misapply the law of anticipation, while its arguments based on Bell are legally unsound and depend entirely on circular reasoning.

First, Samsung accuses Alexion of recycling old expert declarations and failing to respond substantively to Samsung’s arguments and expert opinions. But Samsung, as the Petitioner in this proceeding, set the scope of the entire validity inquiry with its Grounds recycled from the Amgen IPRs. Alexion simply responds to those Grounds accordingly. As Alexion’s experts explained in their declarations accompanying Alexion’s Patent Owner Response, Samsung rehashes substantially the same core art and arguments presented in the 2019 Amgen IPRs, and the prior Alexion declarations substantively address those arguments.

Second, Samsung now reimagines the importance of Tacke in its narrative of the prior art by bringing Tacke (previously a background, supporting reference) to the forefront as the starting point of a POSA’s path to engineering eculizumab.

Samsung’s obviousness combinations—now suddenly rearranged to revolve around Tacken—rest on the false premise that a highly skilled artisan seeking to prepare the eculizumab antibody in 2007, would have ignored the fact that Tacken cited solely to Thomas (which *discloses only an IgG4*) when referencing “eculizamab [sic],” and would have instead misinterpreted Tacken as disclosing eculizumab’s claimed IgG2/IgG4 structure, rather than merely identifying an isotype control for studying anti-DC-SIGN antibodies, *not anti-C5 antibodies*. A POSA looking to identify eculizumab’s structure would likely have not considered Tacken at all (much less started from it), and at best, would have been skeptical of Tacken’s unclear disclosure in this context.

Samsung’s Ground 1, styled as express anticipation by Bowdish (EX1004), fails because a POSA would not have seen any disclosure in Bowdish of the uniquely-engineered C5-binding antibody consisting of SEQ ID NOs: 2 and 4 claimed in the ’880 patent. According to Dr. Ravetch, a POSA would have sought out eculizumab’s sequence by searching the name “eculizumab.” ALXN2104 at 120:15-20, 139:25-140:3. Bowdish, however, does not mention or refer to “eculizumab” even once. The POSA searching for “eculizumab” thus would not have found Bowdish. Moreover, even if a POSA had somehow found Bowdish, Bowdish described a very different compound—a “peptide-mimetic” compound

designed solely for presenting the peptide hormone “TPO” on a neutral “scaffold” to enhance the peptide’s stability and half-life. Bowdish also does not state anywhere that any of its disclosed sequences “binds C5” as required by the ’880 patent. It cannot anticipate.

Samsung’s Grounds 2-5, alleging obviousness, fail because they rely on post-hoc knowledge of the ’880 patent’s unique claimed sequence to reconstruct that invention piecemeal from structurally and functionally distinct compounds in unrelated art. *See Merck Sharpe Dohme B.V. v. Warner Chilcott Co.*, 711 Fed. App’x 633, 637 (Fed. Cir. 2017) (“[U]sing the [patent-in-suit] as a roadmap to piece together various elements of [the prior art] . . . represents an improper reliance on hindsight.”).

Samsung’s Grounds also fail to explain why a POSA would have been motivated to make, or would have reasonably expected success with, the specific pharmaceutical compositions or other dosing and treatment limitations recited in the claims for an antibody that, as far as a POSA knew, might have never been made or tested for C5 binding, *in vitro* activity, therapeutic effect in treating PNH (as the claims require), or suitability for pharmaceutical formulation. Samsung also fails to appreciate the breadth of potential formulations suggested by the

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

Samsung's Ground 6, styled as inherent anticipation, fails because Bell does not inherently, or expressly, disclose all the elements recited in claim 2 of the '880 patent. Samsung cannot prove that it does simply by referring back to its hindsight driven conclusion that the claimed sequence would have been obvious at the time over the prior art sequences combined in piecemeal. That's circular reasoning, not inherent anticipation.

II. ARGUMENT

A. Alexion's Expert Declarations Are Proper, Substantive Responses to Samsung's Recycled Grounds

1. Samsung's Grounds Are Substantially the Same as the Amgen IPRs

As an initial matter, Alexion does not "merely reference old declarations from the Amgen IPR" but rather, fully reincorporates them because of the striking similarity between Samsung's Grounds and Amgen's Grounds in 2019. Although Samsung attempts to distinguish its Grounds from Amgen, because "none of Amgen's Grounds rely on Tacken" (Reply at 2), Amgen cited to Tacken in its '880 petition for the same exact purpose that Samsung does now: its vague and confusing reference to IgG2/G4 as a negative control. *See* IPR2019-00740, Paper 2 at 13-14 (PTAB Feb. 28, 2019) (Arguing that "Tacken explicitly described using h5G1.1-

mAb (5G1.1, *eculiz[a]mab*; Alexion Pharmaceuticals) containing an *IgG2/IgG4 constant region*.”) (internal quotations omitted). Samsung’s reliance on Tacken as a limited, background reference in its original Grounds does not differentiate Samsung’s arguments from those presented by Amgen. Neither does Samsung’s belated attempt to move Tacken to the lead-off hitter position in its Grounds now. That reimagination of Samsung’s Grounds after institution on the Grounds of the petition is improper. *See* Paper 9 at 68. Each prior art reference relied upon by Samsung was relied upon in the same manner by Amgen in 2019. Alexion (and its experts) can only respond to the arguments put in front of it, and here, Samsung’s arguments are recycled from the Amgen IPRs with only minor, insubstantial changes, as shown in the following table:

Reference	Language from Samsung’s ‘880 Petition	Language from Amgen’s ‘880 Petition
Tacken	“Tacken states that h5G1.1-mAb contains the human hybrid IgG2/IgG4 constant domain.” Samsung Petition at 22.	“Tacken explicitly described using h5G1.1-mAb . . . containing an IgG2/IgG4 constant region.” Amgen Petition at 13-14.
Bell	“Bell teaches that eculizumab . . . had been successful in the treatment of PNH.” Samsung Petition at 32.	“Bell taught treating a patient suffering from PNH using a pharmaceutical composition comprising eculizumab.” Amgen Petition at 46-47.

Reference	Language from Samsung's '880 Petition	Language from Amgen's '880 Petition
Bowdish	"Bowdish provides the entire eculizumab amino acid sequence through SEQ ID NOS:67 and 69." Samsung Petition, 24.	"Bowdish provides the complete sequences of the heavy and light chains . . . as SEQ ID NO:67 . . . and SEQ ID NO:69." Amgen Petition, 51.
Evans	"Bowdish provides . . . the incorporation by reference of the heavy chain CDR3 of Evans." Samsung Petition, 24.	"Evans disclosed the eculizumab heavy chain CDR3 region (the missing piece from Bowdish)." Amgen Petition, 30.
Mueller PCT	"Mueller PCT discloses sequences for anti-pVCAM antibodies . . . with the C1 and hinge regions of human IgG2 and the C2 and C3 regions of human IgG4." Samsung Petition, 22.	"Mueller taught methods for making chimeric antibodies containing the C1 and hinge region of human IgG2 and the C2 and C3 regions of human IgG4 . . . (HuG2/G4 mAb)." Amgen Petition, 61.
Wang	"A POSA would know that eculizumab could be successfully and stably formulated . . . in the range of 1 to 30 mg/ml based on the express teachings of Wang, and thus eculizumab could be formulated at 10 mg/ml." Samsung Petition, 48.	"Wang taught eculizumab formulations of between 1 to 30 mg/ml, encompassing the claimed 10 mg/ml concentration." Amgen Petition, 59.

2. Alexion's Experts Provided Proper Expert Opinion Responsive to Samsung's Experts

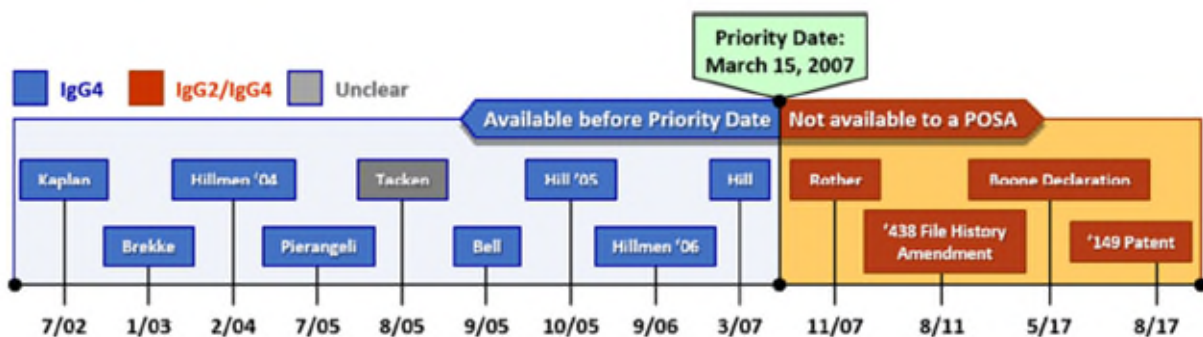
Samsung argues that Alexion's experts submit "no facts, no evidence, and no explanation of any kind" to support their opinions against Drs. Ravetch and Ippoliti.

Reply at 3. This is incorrect and misstates the nature of the opinions expressed by Alexion's experts within their declarations. It's also incorrect that "Alexion's experts never submitted declarations actually responding to" Samsung's experts as Samsung alleges. Reply at 4. Alexion's experts, Drs. Casadevall and Trout, each independently reviewed Samsung's IPR petition regarding the '880 patent, the declarations of Samsung's experts, the Board's Institution Decision regarding the '880 patent, and the documents cited therein. *See* ALXN2105, ¶¶ 6-7; ALXN2107, ¶¶ 6-7. Only after that complete review did Alexion's experts conclude that Samsung relies on "substantially the same core art and arguments presented in the Amgen IPRs." ALXN2105, ¶ 6; ALXN2107, ¶ 6. Drs. Casadevall and Trout therefore felt it was appropriate to respond to Samsung's experts with precise reference to the relevant sections of the detailed expert opinions they provided in response to the same art and arguments in the 2019 Amgen IPRs. Contrary to Samsung's mischaracterization, Alexion's Response is much more than "pure attorney argument" (Reply at 4), but rather, argument supported by extensive and detailed expert opinion and consideration responding to Samsung's recycled arguments from the prior IPRs. *See supra* Section II(A)(1).

B. Samsung Manufactures its Prior Art Narrative Entirely From Hindsight

Samsung's prior art narrative and convenient sequence alignments could not exist for a POSA without the benefit of hindsight. Armed with the claimed sequence as a guide, Samsung and its expert Dr. Ravetch, set out to piece together eculizumab's SEQ ID NOs: 2 and 4 using disparate combinations of prior art references. ALXN2108 at 46:16-22 (Dr. Ravetch's "mission" was to "identify if the prior art disclosed the sequence of eculizumab" and determine whether a POSA "could derive a sequence that would be identical to eculizumab.")). Despite the overwhelming evidence identifying "eculizumab" as an IgG4 antibody, Samsung continues to cling to the supposedly "*clear* teachings of Tacke" (Reply at 5) which is unrelated to C5 binding (*see* Paper 13 at 18), and cites solely to Thomas (an IgG4 antibody) for support of its single, misspelled reference to eculizumab. EX1008 at 011; ALXN2108 at 43:21-44:10, 63:18-22. Tacke, however, would not have changed a POSA's understanding that "eculizumab" was an IgG4 isotype antibody. For one, Tacke was not the "culminat[ion]" of a "clear, and linear path" of prior art as Samsung chooses to describe it (Reply at 5). The literature *after* Tacke identified "eculizumab" as Thomas's IgG4 antibody. EX1007 at [0052]; EX1013 at 009 (referring to what "[e]culizumab is" and citing to Thomas as reference number 9); EX1014 at 002 (referring to what "[e]culizumab (Soliris, Alexion Pharmaceuticals)

is” and citing to Thomas as reference number 13); ALXN2028 at 31, n. 6. Moreover, Tacken does not cite, nor is it cited by, any of the other references in Samsung’s Grounds. Tacken is at best a lone, confused voice in the wilderness. Unsurprisingly, that is not the current legal standard for obviousness.



Tacken also does not show that “eculizumab” was known as an IgG2/IgG4 isotype, as Samsung purports. It’s unclear whether a POSA would have even considered Tacken, but if they had, the prior art “viewed *as a whole*” repeatedly indicated that “eculizumab is” Thomas’s IgG4 antibody. *See, e.g., Impax Lab’s Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379 (Fed. Cir. 2018); *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) (“One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.”); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (“The full field of the invention must be considered . . . including that which might lead away from the claimed invention.”). Samsung’s new-found fixation on Tacken, to the

exclusion of the art as a whole, is improper, and betrays the true nature of Samsung's obviousness exercise as a hindsight-based jigsaw puzzle.

Moreover, a POSA motivated to recreate "eculizumab" for the treatment of PNH would not have disregarded the clinical literature demonstrating its success and focused on a single statement buried in Tacke – a publication concerning "anti-DC SIGN" antibodies for vaccination strategies. *See Impax*, 893 F.3d at 1379-80 (discounting reference that, "as a whole," was "not about" and "barely mentioned" the claimed compound). Because Tacke itself cites to Thomas, the most reasonable reading would have been that "eculizumab" was an **IgG4** antibody, as the literature consistently cited Thomas for "eculizumab".

Moreover, Samsung's argument that "Thomas does not even contain the word eculizumab" (Reply at 5) is irrelevant because: (1) nothing in Thomas expressly rules out eculizumab as an antibody discussed therein (ALXN2108, 61:15-24), and (2) it ignores the way Samsung's own cited literature viewed Thomas. The following table exemplifies Samsung's cited literature that described "eculizumab" as Thomas's IgG4 antibody:

Samsung's Exhibit	Relies on Thomas's IgG4 as "Eculizumab"	Statement Identifying "Eculizumab" as Thomas's IgG4
Hillmen 2004 (EX1011) at 553	✓	In reporting on a Phase II clinical trial for PNH, cites <i>Thomas</i> , 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 (EX1013) at 2559	✓	In reporting on a Phase II clinical trial for PNH, cites <i>Thomas</i> , Ref. No. 9, as describing "[e]culizumab" as "a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage."
Hillmen 2006 (EX1014) at 1234	✓	In reporting on a Phase III clinical trial for PNH, cites <i>Thomas</i> , Ref. No. 13, as describing "[e]culizumab" as "a humanized monoclonal antibody directed against the terminal complement protein C5."
Bell (EX1007) at [0052]	✓	In a patent application describing results of Phase II clinical trials for PNH, cites <i>Thomas</i> as describing "[m]ethods for the preparation of h5G1.1-mAb," also identified "under the tradename eculizumab."

Samsung's Exhibit	Relies on Thomas's IgG4 as "Eculizumab"	Statement Identifying "Eculizumab" as Thomas's IgG4
Kaplan (EX1023) at 1018	✓	Cites <i>Thomas</i> , Ref. No. [258884], for synthesis of "[h]umanized 5G1.1," also identified as "eculizumab."
Tacken (EX1008) at 1279	✓	Cites <i>Thomas</i> , Ref. No. 19, as describing the antibody "h5G1.1-mAb (5G1.1, eculizumab; Alexion Pharmaceuticals)"

It would be unreasonable for a single isolated, ambiguous sentence in Tacken to upend a POSA's understanding of "eculizumab" from the consistent teachings before and after it in the art. But once Samsung found Tacken, it simply chose to end its prior art search. ALXN2108 at 50:13-18 (Dr. Ravetch "didn't feel it was necessary" to review the prior art after Tacken because he "had the Tacken reference."). It is therefore Samsung, not Alexion, who views "a POSA as a simpleton" (Reply at 7) for attributing undue weight to the inconclusive disclosure of Tacken, without considering its context within the art as a whole.

C. Samsung's Ground 1 Fails Because It Cannot Show Bowdish Anticipated Claim 2

Samsung's Ground 1 contends that claim 2 was anticipated by Bowdish. But Bowdish alone does not disclose the claimed sequence. And Bowdish's limited incorporation by reference of the "[c]onstruction of 5G1.1" in Evans, the

parental mouse monoclonal antibody, and the only full antibody sequence disclosed in Evans, would direct a POSA to a murine framework sequence, not the claimed sequence.

Samsung continues to overread Bowdish’s single reference to Evans for “[c]onstruction of 5G1.1” (Reply at 8)—a mouse antibody whose sequence is nowhere close to the uniquely-engineered humanized antibody claimed in the ’880 patent. That reference appears in Example 4 of Bowdish, which states: “The TPO mimetic peptide graft in Fab clone X4b has been transplanted into the heavy chain CDR3 region of another antibody framework, 5G1.1 Construction of 5G1.1 is described in U.S. Application Ser. No. 08/487,283 incorporated herein by reference.” EX1004 at [0191]. Notably, the statement does not incorporate any of Evan’s scFv sequences, including the HCDR3 sequence admittedly missing from Bowdish. Samsung cannot rewrite Bowdish’s limited reference to construction of Evans’s “5G1.1” mouse antibody as an open-ended incorporation of Evans’ entire 93-page disclosure, including sequences for humanized fragments that are not the “5G1.1” antibody, let alone precise sequences to then insert into a precise location into the antibody disclosed in Bowdish. Thus, Bowdish cannot anticipate. *See* ALXN2022, ¶¶ 209-218.

Even if Samsung were correct to read Bowdish as incorporating Evans in its entirety (which it does not) Samsung still cannot show how Bowdish anticipates the '880 patent, when the presently claimed antibody is not disclosed anywhere in the two references, alone or combined. Instead, Samsung attempts to recreate the '880 patent's novel, unique claimed sequence by mixing and matching sections of sequences plucked from Bowdish's full-length TPO-mimetic compound, and structurally distinct "scFv" compounds from Evans. That cannot be anticipation, which requires that "the prior art reference. . . show[s] the claimed invention arranged or combined in the same way as recited in the claim." *Net MoneyIN v. Verasign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008); *Therasense, Inc. v. Beckton 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.").

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

Samsung's Ground 2 fails because Samsung has failed to show how, without hindsight, a POSA would have been motivated to select and combine Bowdish and Evans, in view of Bell, Tacke, and Mueller PCT, to obtain the claimed invention, or how they could have reasonably expected to succeed in doing so. In its Reply,

Samsung alleges that Alexion “does not dispute” that the “Bowdish/Evans integrated disclosure expressly discloses the claimed sequences, as shown in alignments.” Reply at 10-11. Alexion disagrees with the hindsight characterization of Bowdish and Evans as a single integrated document, as Bowdish’s incorporation by reference of Evans is limited to the 5G1.1 murine construct (EX1004 at [0191]), and a POSA would have had no reason to combine Bowdish’s TPO-mimetic construct with one of the many sequences disclosed within Evans. *See* ALXN2022, ¶¶ 208-223.

Samsung’s “obviousness rationale” also mischaracterizes how a POSA would have viewed the teaching in the art. Samsung claims that from Bell, “a POSA would have been led first to *Evans and Thomas*.” Reply at 11. This is incorrect. Although Bell cites Evans, Bell refers to the preparation of both “h5G.1.1-mAb” and “*h5G1.1-scFv and other functional fragments*.” EX1007 at [0052]. Evans discloses the preparation of *humanized 5G1.1-scFv and other functional fragments*. EX1005 at 42:55-49:48. Further, Evans never refers to “*h5G1.1-mAb*.” Instead, Evans refers to “5G1.1 mAb,” which is the native mouse antibody. EX1005 at 50:3 (“the native *murine* 5G1.1 mAb”). Thomas, in contrast, discloses the preparation of “*h5G1.1-mAb*.” EX1010 at 013 (referring to the avidity of “h5G1.1 HuG4,” which Thomas also refers to as “humanized *h5G1.1 mAb*”). Bell then refers only to “*h5G1.1-mAb*” (*i.e.*, Thomas’s antibody) as “undergoing clinical trials under the tradename

eculizumab.” EX1007 at [0052]; ALXN2108 at 41:7-42:7. Thus, Samsung’s “obviousness rationale” depends on a gross misreading of the prior art.

Samsung also assumes, in circular fashion, that a POSA would have immediately recognized that “Thomas’ full-length IgG4 antibody is not eculizumab, based on the express (and more recent) teaching of Tacke that eculizumab has an IgG2/IgG4 domain.” Reply at 11. This argument must also fail without the benefit of hindsight, because the art as a whole, taught that “eculizumab” had an IgG4 constant region as described in Thomas. Nor is it anywhere close to as clear as Samsung alleges that “Tacke expressly disclosed that eculizumab was an IgG2/G4.” Reply at 12. As previously explained (*see supra* Section II(B)), Tacke only cited to Thomas, an IgG4 antibody, for its singular reference to “eculizumab [sic].” EX1008 at 1279.

Even putting aside Samsung’s requirement that a POSA ignore the art’s direction towards Thomas and “continu[e] to search for relevant literature of the 5G1.1 antibody” (Reply at 11), nothing would have guided a POSA to turn from Bell to Bowdish for the structure of “eculizumab.” Samsung assumes that a POSA considering the structure and sequence of Bell’s “eculizumab,” would have (1) selected Bowdish, rather than Thomas, as a starting point despite the fact that Bowdish **never mentions “eculizumab,” is not cited by Bell** or any other prior art

references defining “eculizumab,” and **does not contain any C5-binding or clinical data** suggesting that it might be associated with “eculizumab”; (2) identified Bowdish’s TPO-mimetic compound as relating to a humanized antibody with a hybrid IgG2/IgG4 constant region even though nothing in Bowdish contains such a statement; and (3) associated the purported IgG2/IgG4 structure of Bowdish’s TPO-mimetic compound with “eculizumab” despite the teaching in Bell itself, and the consistent teaching throughout the prior art, that a POSA would have understood “eculizumab” to be an IgG4 isotype antibody, which would not match with the sequence of a hybrid IgG2/IgG4 antibody.

Here, Samsung uses its present-day knowledge of the ’880 patent and 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, and certainly wouldn’t have turned to first. At the same time, Samsung ignores the art’s consistent teaching that “eculizumab” had an IgG4 constant region as described in Thomas. For this reason, Samsung’s Ground 2 must fail.

E. Samsung’s Ground 3 Fails Because It Cannot Show That Claim 2 Is Obvious Over Evans and Mueller PCT in View of Bell and Tacken

As with Ground 2, Samsung attempts to combine Evans and Mueller PCT to arrive at the claimed sequence. This combination also fails because the only actual antibody disclosed in Evans is **the 5G1.1 murine antibody** and Mueller PCT relates to an **entirely different antibody directed at “pVCAM.”** As the Board previously noted in IPR2019-00739, Mueller PCT identified *only* an ***IgG4*** isotype antibody (*i.e.*, the isotype of Thomas) as an anti-C5 antibody and taught nothing about the C5 binding or clinical properties of “h5G1.1 CO12 HuG2/G4 mAb,” which Mueller PCT uses only as a negative control. Paper No. 15 at 57.

Nor would a POSA have been motivated to combine the sequences in Evans and Mueller PCT—neither of which cites to the other—in the exact manner to get the specific claimed antibody sequence of the ’880 patent. As the Board correctly recognized in the Amgen IPRs, nothing in Evans or Mueller instructs whether or how such a combination should be done, including “precisely those portions of Evans’s and Mueller’s constructs to create an antibody having exactly the sequences set forth SEQ ID Nos: 2 and 4.” IPR2019-00740, Paper No. 15 at 57. In its institution decision, this Panel provided no comment on how Samsung’s combination of Evans and Mueller improves upon the same combination presented

in the Amgen IPRs. There, this Panel rejected the combination of Evans and Mueller, and credited the same arguments from Alexion that it apparently finds unpersuasive now. Accordingly, this Panel should reach the same result now as it did in the Amgen IPRs and reject this combination.

Just as in Ground 2, even if a POSA were somehow motivated to combine these disparate references, viewing them in light of the Bell and Tacke references of Ground 3 would have led the POSA even further astray, as both of those references cited to Thomas's HuG4 sequence for the sequence of the anti-C5 antibody, eculizumab. As already noted, Bell's reference to "h5G1.1-mAb" is a reference to the antibody disclosed in Thomas. EX1010 at 013 (referring to the avidity of "h5G1.1 HuG4," which Thomas also refers to as "humanized h5G1.1 mAb"). Like Bell, Tacke refers to "h5G1.1-mAb" then cites to Thomas. Further, Tacke's negative control that supposedly "contain[s] the same IgG2/IgG4 constant region" is referring to Mueller 1997's IgG2/IgG4 negative control, and there is nothing in either Mueller reference that suggests that its negative control antibody retained anti-human C5 activity after Mueller overhauled that antibody's structure to have the hybrid IgG2/G4 constant region. *See* Paper 13 at 32-33.

F. Samsung’s Grounds 4 and 5 Fail Because It Cannot Show That Claims 1 and 3 Are Obvious Over Grounds 2 and 3 Further Combined with Wang

Samsung’s invalidity arguments similarly fail against the dosing and formulation limitations of claims 1 and 3. With nothing in Bell, Bowdish, or Evans rendering obvious an antibody with the specific sequence recited in the claims of the ’880 patent, a POSA would not have been motivated to make, or reasonably expected to succeed in making, a “pharmaceutical composition” of such an uncharacterized antibody. *See* ALXN2024, ¶¶ 64-91; ALXN2022, ¶¶ 189-91. A POSA particularly would have had no reasonable expectation of success, to formulate an uncharacterized antibody having a novel, hybrid “IgG2/IgG4” constant region when nothing in the literature reported the formulation or testing of such an antibody, on a commercial or experimental scale. ALXN2024, ¶¶ 69-75.

Nor would Bell or Wang have motivated a POSA to make the specific composition of claims 1 and 3—“a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution”—or have given a POSA a reasonable expectation of success in doing so. Bell described no specific pharmaceutical compositions, and only suggested that an undefined composition was used for purposes of administering “eculizumab” by intravenous infusion to treat PNH. ALXN2024, ¶¶ 78; ALXN2022, ¶¶ 190-191. A POSA would not have been

motivated to combine Bell's teachings of an undefined composition *for injection* with Wang (EX1044), which broadly concerned administration of a wide range of anti-C5 antibodies and fragments *by inhalation through a "nebulizer"* device for treating respiratory diseases. EX1044, ¶¶ [0169]-[0173]; ALXN2024, ¶¶ 81-83. *See, e.g., Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013).

Further, nothing in Wang disclosed a pharmaceutical composition containing a "10 mg/ml antibody solution" of "eculizumab" in a "single-use dosage form." ALXN2024, ¶¶ 80. Wang also did not specifically teach "concentrations in the range of 1 to 30 mg/ml" as Samsung claims (Petition at 48) but rather suggested wide ranges including 1-30 mg/ml, 40-200 mg/ml and 1-200 mg/ml that hypothetically might be used *for nebulization* of various unrelated "anti-C5 antibodies. EX1044, ¶¶ [0067], [0130], [0170]-[0172], Fig. 10; ALXN2024, ¶¶ 84-86.

Similarly, nothing in Bell disclosed a "300 mg single-usage dosage form." ALXN2106 at 32:11-14. Bell disclosed the administration of 600 mg and 900 mg dosages, but did not describe any particular dosage units or dosage forms. ALXN2024, ¶¶ 91; ALXN2106 at 32:4-10.

To arrive at the specific composition of claims 1 and 3, Samsung argues that a 300 mg dose would have been obvious because 300 is a "common factor of 600 and 900," and "[b]ased on simple arithmetic, 30 ml of a 10 mg/ml solution provides

a 300 mg total dose.” Petition at 47-48. Both Dr. Ippoliti and Dr. Ravetch agreed that Bell suggests many total dosages, because 600 and 900 are divisible by “many other numbers” (ALXN2104, 200:16-18; ALXN2106, 45:21-46:5), and Wang teaches a “whole range” of concentrations (ALXN2104, 202:24-203:6; ALXN2106, 45:11-16). Dr. Ippoliti also agreed that a POSA could have reasonably followed a number of paths from Bell and Wang using such simple arithmetic. ALXN2106 at 65:4-11. For example, Dr. Ippoliti acknowledged that formulations comprising a 100 mg total dose using 25 ml of a 4 mg/ml solution, and a 150 mg total dose using 30 ml of a 5 mg/ml solution are taught by the combination of Bell and Wang. ALXN2106, 63:24-64:25.

Samsung attempts to argue that “Alexion did not bother to submit any expert testimony specifically rebutting the opinions of Dr. Ippoliti or Dr. Ravetch as to why the dosing and formulation limitations were obvious.” Reply at 22-23. But Dr. Trout’s declaration explained that his prior 2019 declaration was responsive to the recycled arguments and opinions presented by Samsung and its experts. ALXN2107, ¶¶ 7-8; ALXN2024.

G. Samsung’s Ground 6 Fails Because It Cannot Show that Claim 2 Is Anticipated by Bell

Samsung’s Ground 6 fails because Bell does not expressly or inherently disclose all the elements recited in claim 2 of the ’880 patent. *See, e.g., Teleflex,*

Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1335 (Fed. Cir. 2002) (“[A]nticipation requires that each limitation of a claim must be found in a single reference . . . [and] does not permit an additional reference to supply a missing claim limitation.”); *Therasense, Inc. v. Becton Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) (“Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim.”). Samsung openly admits that “Bell’s disclosure does not include the exact amino acid sequence of eculizumab” Petition at 33. As the Board has previously admitted, Bell cannot anticipate because: (1) “Bell uses the word ‘eculizumab’ at least 25 times throughout its disclosure, describing it as an anti-C5, h5G1.1-mAb, but without further expressly describing its structure” (Paper No. 9 at 55); and (2) although Bell discusses eculizumab as a “particularly useful . . . therapy for PNH patients,” it never expressly describes what eculizumab is. Paper No. 9 at 55. In order to “describe[] its structure,” Samsung must cobble together multiple unrelated references. That is an analysis for an obviousness theory, not anticipation.

With respect to Bell, in contrast to the facts of *In re Crish*, 393 F.3d 1325 (Fed. Cir. 2004) (“*Crish*”), “eculizumab” was not a “known” antibody for which the sequence could have been determined. *See Endo*, 894 F.3d at 1378-79. As the Boone Declaration explained, the identity of the sequence and composition of the

antibody product used in the clinical trials published as Bell was confidential. EX1002 at 1433-34. 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. EX1002 at 1385-88. Moreover, a POSA attempting to determine the sequence of “eculizumab” as described in Bell would have followed those publications’ references to Thomas and arrived at the IgG4 antibody that Thomas described—an antibody having a very different sequence than the one recited in the ’880 patent. Accordingly, *Crish* is distinguishable on the facts.

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

antibody described in the prior art is **not** the claimed antibody. *See, e.g.*, ALXN2022 at ¶¶ 174-184. Thus, *Nichols* also fails to support a finding of inherent anticipation.

A POSA could read Bell a million times and not find the sequence of eculizumab. The sequence and composition used in the Bell clinical trials was strictly confidential. One can only accept Samsung's argument by positing that, despite all this, the sequence would have been obvious to a POSA in view of the prior art. That is definitively **not** inherent anticipation.

H. Objective Indicia of Non-Obviousness Support a Finding of Validity

Samsung's continued denial of the existence of objective indicia of non-obviousness is just a rehashing of its prior art obviousness arguments (Petition at 55-58). Samsung argues that the strong indicia of non-obviousness here don't count because eculizumab and its sequence were already known in the art. But that is, of course, circular. There is no dispute that the indicia of non-obviousness here are due to the specific composition of the uniquely-engineered, claimed sequences.

Objective indicia of non-obviousness, 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). The indicia of non-obviousness "are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known

elements.” *Id.* Such evidence must receive fair and full consideration. *Graham*, 383 U.S. at 36.

SOLIRIS[®], the commercial embodiment of the ’880 patent, is a resounding commercial success—having generated substantial sales in the relevant market (Paper 13 at 68-69). *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). The outstanding economic performance of SOLIRIS[®] has a direct nexus to the uniquely-engineered, patented features of the ’880 patent. *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—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 significant industry praise for its innovation. *See* Paper 13 at 69.

Samsung improperly relies on *Ormco Corp v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006) to rebut the presumption of nexus between SOLIRIS[®] and the claimed invention. In *Ormco*, experts testified that “commercial success was due to unclaimed or non-novel features of the device.” *Id.* at 1312. No such

testimony exists in this case, because the unique claimed sequences are “the successful feature of the claimed invention,” and contrary to the arguments in Samsung’s Grounds, the claimed sequences were novel and non-obvious at the time of the invention.

III. CONCLUSION

Alexion respectfully submits that the Board confirm the patentability of claims 1-3.

Respectfully submitted,

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CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing **PATENT OWNER'S SUR-REPLY** and **EXHIBIT ALXN2108** were served via electronic mail on July 26, 2024, 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 SUR-REPLY** specified in 37 C.F.R. § 42.24 has 5,592 words, in compliance with the 5,600 word limit set forth in 37 C.F.R. § 42.24.

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