UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2019-00739
U.S. Patent No. 9,725,504 B2

PETITIONER'S REPLY TO PATENT OWNER RESPONSE

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I. Introduction

As the Petition demonstrated, Alexion publicly disclosed eculizumab's amino acid sequence—including its hybrid IgG2/IgG4 constant region—years before Alexion's claimed March 15, 2007 priority date. Alexion cannot now reap the benefits of patent protection for the very same subject matter it already placed in the public domain.

There is *no dispute* that, before March 15, 2007, a POSA would have understood that the nonproprietary name *eculizumab* refers to "one – and only one – specific antibody as defined by its unique amino acid sequence." Paper 22, 14; *see also*, ALXN2022, ¶¶101, 143; AMG1081, ¶¶7, 13-18. Thus, a POSA before March 15, 2007, would have known that Alexion's clinical trial publications such as Hillmen, Bell, Hill '05, and Hillmen '06—which each discloses treating PNH patients with intravenous pharmaceutical compositions comprising eculizumab—each refers to the same, single antibody, having "one – and only one" amino acid sequence. AMG1004, 552; AMG1005, ¶[0082]; AMG1047, 2559; AMG1012, 1233; AMG1034, 1279; AMG1021, 1017; AMG1019, 56; AMG1081, ¶¶5-12, 32-36, 59-60; Paper 22, 14.

Further, there is *no dispute* that the eculizumab antibody reported in Alexion's clinical trial publications did indeed possess the amino acid sequences provided in SEQ ID NOs. 2 and 4 of the '504 patent. Indeed, Alexion admitted to

the USPTO that "the antibody (eculizumab) used in each of the studies … *contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4*."[1] AMG1014, 767(¶6). And Alexion now confirms this in its POR, stating that "it is known today that *SOLIRIS as used in these studies had the claimed sequence* of *SEQ ID NOs: 2 and 4*…." Paper 22, 31.

The primary issues of dispute in this matter thus boil down to (i) whether a POSA before March 15, 2007 would have known or been able to determine from the art, the amino acid sequence of eculizumab; and (ii) whether the claimed 300 mg single-use formulation of 30 ml in a 10 mg/ml concentration would have been obvious. Alexion's POR obscures these issues by asserting incorrect legal standards and mischaracterizing the knowledge in the prior art.

First, Alexion argues that Hillmen does not inherently anticipate the challenged claims because a POSA would not have *necessarily* determined the amino acid sequence of eculizumab from the information publicly available as of the priority date. Paper 22, 34. But long-standing precedent makes it clear that "*recognition* by a person of ordinary skill in the art before the critical date … *is not required* to show anticipation by inherency." *Schering Corp. v. Geneva Pharms.,* 339 F.3d 1373, 1377 (2003). Alexion's admission that Hillmen "necessarily" includes the claimed sequences of SEQ ID NOs: 2 and 4 is binding and dispositive,

[1] Emphasis is added throughout this Reply, unless otherwise noted.

given that there was sufficient information in the prior art—including in Alexion's own publications—that would have allowed a POSA to make and use eculizumab before March 15, 2007. AMG1014, 767(¶6); Paper 22, 31; Paper 2, 26-31.

Second, Alexion applies flawed obviousness analyses, centered on a mischaracterization of a POSA's view of the prior art. Alexion's nonobviousness position is based on its argument that the prior art disclosed that "'eculizumab is' Thomas's IgG4 antibody." Paper 22, 14-19, 26-27. This is patently false. *None* of the references Alexion cites discloses that "eculizumab *is* Thomas's IgG4 antibody," nor do any of those references link an isotype to eculizumab, let alone an IgG4 isotype. In fact, the only reference of record that expressly links *any* isotype with the term eculizumab is Tacken, which discloses that eculizumab is an IgG2/IgG4 antibody. Paper 2, 17; AMG1002, ¶46; AMG1034, 1279.

Amgen's Petition showed by a preponderance of the evidence that every challenged claim is unpatentable over the asserted art. Alexion's POR changes nothing as it fails to overcome the great weight of evidence shown in the Petition. The Board should accordingly cancel the challenged claims as unpatentable.

II. Alexion's admissions confirm that Hillmen inherently anticipates the challenged claims.

There is no dispute that Hillmen explicitly disclosed each and every element of challenged claims 1-3 and 7-10, arranged as claimed, except for the amino acid sequences of SEQ ID NOs: 2 and 4. Paper 2, 25-37; AMG1002, ¶¶75-96; Paper 22,

32-34. But, Alexion admitted that the eculizumab Hillmen administered to PNH patients inherently possessed the amino acid sequences of SEQ ID NOs: 2 and 4. Alexion admitted this in statements made to the USPTO and has now reaffirmed this fact in its POR. Paper 22, 31 ("it is known today that *SOLIRIS as used in these studies had the claimed sequence* of SEQ ID NOs: 2 and 4."); *see also, id.*, 34 ("today … it is known that the clinical studies underlying Hillmen *actually* used an antibody with [the claimed sequences]."); AMG1015, 736, 738(¶6).

Faced with its own admission, Alexion argues that there can be no inherent anticipation "if a POSA *could not have necessarily determined* the later claimed structure/composition from the information publicly available as of the priority date." Paper 22, 34 (citing *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374 (Fed. Cir. 2018)). But, Alexion misinterprets the law which has long held that "recognition by a person of ordinary skill in the art before the critical date of the [challenged] patent is *not required to show anticipation by inherency*." *Schering*, 339 F.3d at 1377; *see also, In re Omeprazole Patent Litigation*, 483 F.3d 1364, 1373 (Fed. Cir. 2007) ("[i]nherency is not necessarily coterminous with knowledge of those of ordinary skill in the art. Artisans of ordinary skill *may not recognize the inherent characteristics* or functioning of the prior art."); *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) ("Because [the claim limitation] was inherent in the prior art, *it is irrelevant that the prior art did not recognize the*

key aspect of [the] invention."). Alexion admits that the claimed amino acid sequences are necessarily present in Hillmen's disclosure of eculizumab, and the Petition showed that Hillmen is enabling in light of the general knowledge in the art. Paper 22, 26-31.

Alexion's reliance on *Endo* (an *obviousness* case, not anticipation) and *Bayer CropScience LP v. Syngenta Ltd.*, IPR2017-01332, Paper 15 (PTAB Apr. 2, 2018) (a non-precedential Board decision) is misplaced and does not compel finding a lack of inherency here. In *Endo*, the question arose as to whether a claimed vehicle formulation was inherently disclosed in a prior art reference. *Id.*, 1381-1383. But, the pharmacokinetic data disclosed in the reference was not attributable to the claimed vehicle (it was attributable to the *active ingredient*, testosterone), and there was no evidence in the art to preclude the possibility of a different vehicle being used in the prior art reference. *Id.*, 1381. Here, the successful treatment of PNH patients disclosed in Hillmen is attributable to the active ingredient: eculizumab. AMG1004, 557-558. And Alexion admits that "the sole active ingredient in SOLIRIS®" is the "antibody comprising SEQ ID NOs: 2 and 4, which is *responsible for the remarkable clinical properties* of SOLIRIS®…." Paper 22, 64.

Alexion's reliance on *Bayer* also misses the mark. Paper 22, 34. In *Bayer*, the prior art reference referred to the claimed compound by the experimental code

name "KIH-485," but did not provide any information about the chemical structure, chemical formula, or other proprietary information about the compound. *Id.*, 5. The present facts are different because, unlike the asserted reference in *Bayer*, Hillmen discloses using *eculizumab*, not a chemical compound with an experimental code name. AMG1004, Abstract. And as Alexion makes clear, a POSA would have understood that the name eculizumab refers to "one – and only one – specific antibody as defined by its unique amino acid sequence," which is that of SEQ ID NOs: 2 and 4. Paper 22, 14.

Alexion's confirmation that a POSA would understand eculizumab to refer to a single antibody, having a unique amino acid sequence also counters the Board's preliminary conclusion on Institution that "'eculizumab' referred to and refers to a class or category of anti-C5 antibodies…." Paper 15, 33. Given this, the Board was wrong to dismiss Amgen's reliance on *In re Crish*, 393 F.3d 1253 (Fed. Cir. 2004), which compels a finding of inherency here. *Id.*; Paper 2, 25-31; *see also*, AMG1081, ¶¶37-39.

Alexion's remaining defense against the inherency showing here is that the Petition "must go outside the four corners of the references themselves" to show the inherent feature. Paper 22, 33-34. Not so. The Petition points to other references solely to demonstrate the knowledge in the art showing that Hillmen's disclosure fully enabled the claimed method. Paper 2, 29-32.

III. Alexion fails to overcome the prima facie obviousness established in the Petition.

The Petition showed that the challenged claims would have been obvious in view of the asserted art in Grounds 2-7. Paper 2, 37-71; AMG1002, ¶¶97-209. Grounds 2-7 each include Hillmen and/or Bell, and it is undisputed that each of Hillmen and Bell disclosed successfully treating PNH patients with pharmaceutical compositions comprising eculizumab. Paper 2, 13-16. Dr. Casadevall testified that Hillmen reported "on the *successful use of* '*eculizumab*' … to *treat PNH* in a human clinical trial" and Dr. Trout agreed at deposition that Hillmen "provides a pharmaceutical composition to patients" with "some degree of *stability*." ALXN2022, ¶176; AMG1078, 125:11-25; *see also, id.* at 133:15-135:6. As Dr. Balthasar explains, Alexion's repeated public disclosures of successful eculizumab PNH clinical trials, coupled with the other asserted references in Grounds 2-7, would have motivated a POSA to make and use a pharmaceutical composition comprising eculizumab for the treatment of patients with PNH as claimed, with a reasonable expectation of success. AMG1002, ¶¶99, 122-123, 173-174; AMG1081, ¶¶40-42, 59, 85-86, 95.

Alexion bases its nonobviousness position on the tenuous argument that a POSA thought eculizumab is "the IgG4 antibody of Thomas," and thus, according to Alexion, would have had no reason to make the actual eculizumab containing an IgG2/IgG4 constant domain or pharmaceutical compositions comprising

eculizumab with any reasonable expectation of success. Paper 22, 14-27. Alexion's argument does not hold up in view of the evidence. *None* of the references Alexion relies upon discloses that "eculizumab is" Thomas's IgG4 antibody, or any other isotype for that matter. Indeed, Thomas does not even disclose eculizumab. AMG1077, 186:19-22. The only reference of record that expressly links *any* isotype to eculizumab is Alexion's Tacken publication, which discloses that eculizumab has an IgG2/IgG4 constant region. AMG1034, 1279; AMG1002, ¶¶46-47; AMG1081, ¶¶19-25.

A. The evidence does not support Alexion's argument that "eculizumab is the IgG4 antibody of Thomas."

The parties agree that once an antibody is assigned a nonproprietary name like eculizumab, that name refers to "one—and only one—specific antibody as defined by its unique amino acid sequence." Paper 22, 14; ALXN2022, ¶101; AMG1077, 125:5-17; AMG1081, ¶¶16-18. The Parties dispute whether a POSA would have considered the "one—and only one" eculizumab to have the IgG2/IgG4 hybrid constant region as expressly taught in the art and as shown in the Petition, or to have an IgG4 constant region as Alexion attempts to piece together from prior art that says no such thing. The former is true.

The only reference of record that expressly ties an isotype to eculizumab is *Tacken*, which expressly discloses that "h5G1.1-mAb (5G1.1, eculizamab [*sic*]; Alexion Pharmaceuticals) contain[s] the same IgG2/IgG4 constant region" as

Tacken's experimental antibody. AMG1034, 1279; AMG1002, ¶46; Paper 2, 17. Alexion argues that Tacken is "ambiguous" and has "nothing to do with C5 binding," but those arguments fail. Paper 22, 27. The PTAB already correctly rejected Alexion's argument that Tacken is nonanalogous art. Paper 15, 30. Moreover, Tacken is not ambiguous. It expressly discloses that eculizumab "contain[s] the same IgG2/IgG4 constant region" as Tacken's experimental antibody, and a POSA would not have been concerned about Tacken's minor typographical misspelling of eculizumab. AMG1034, 1279; AMG1002, ¶46; AMG1081, ¶¶19-25; AMG1077, 134:25-135:5.

Further, Alexion *admitted* to the USPTO that "*h5G1.1* … [was] well-known to one of ordinary skill in the art *as eculizumab*," and that "it was well-known to one of ordinary skill in the art at the time of filing of priority applications [in 2002] that e*culizumab has a G2/G4 Fc portion*, i.e., a mutated Fc portion." AMG1049, 838-839; Paper 2, 16-17. Alexion attempts to distance itself from these admissions by arguing that they are "non-prior art statements" and "not related to the '504 patent." Paper 22, 51. But the Petition cited these statements as *admissions* by Alexion confirming prior art knowledge about eculizumab, not as prior art statements themselves. Alexion's admissions were not made with regard to claim construction or some unrelated issue, they were made regarding general knowledge in the art about eculizumab, and such admissions are binding on Alexion. *See e.g.*,

Apple Inc. v. Motorola Inc., 757 F.3d 1286, 1290 (Fed. Cir. 2014), *overruled on other grounds* (holding a patentee to statements made during prosecution of a later-filed Japanese application because "the statements were made in an official proceeding" where the patentee "had every incentive to exercise care in characterizing the scope of its invention."); *see also*, *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996).

Sidestepping the express disclosure in Tacken, Alexion and Dr. Casadevall would have the Board believe that eculizumab "was consistently identified as Thomas's IgG4 antibody," but no evidence supports such statements. Paper 22, 19, 26; ALXN2022, ¶123; AMG1081, ¶¶26-31. It is notable that *none* of the references Alexion relies upon expressly discloses *any isotype* for eculizumab, let alone an IgG4 isotype. Paper 22, 16-18; AMG1004, 553; AMG1047, 2559; AMG1012, 1234; AMG1005, ¶[0052]; AMG1021, 1018; AMG1019, 56; AMG1020, 2123; ALXN2028, 31; AMG1081, ¶¶26-27. Alexion's failure to provide such a reference here speaks volumes. Unable to provide any supporting evidence, Alexion instead stitches together a patentability argument of what "eculizumab is" through baseless inferences and hindsight by latching onto Thomas, one of the earliest disclosures of humanizing the murine 5G1.1 antibody. As Dr. Balthasar explains, a POSA reading the prior art as whole would have understood that the references citing Thomas refer to Thomas not for disclosing

what "eculizumab *is*," but for disclosing methods of humanizing antibodies such as 5G1.1, or that eculizumab is a 5G1.1 antibody that binds C5. AMG1002, ¶¶43-49; AMG1081, ¶¶28-30. For example, Dr. Balthasar explained at deposition that Hillmen cites both Thomas *and* Riechmann, and that both references described methods of *humanizing* antibodies. ALXN2032, 79:4-14, 126:12-18. Dr. Casadevall argues in his declaration that "the only reasonable conclusion" for a POSA is that "Thomas in fact described 'eculizumab,'" but when cross-examined Dr. Casadevall admitted that "Thomas does not mention eculizumab anywhere." AMG1077, 186:19-22; ALXN2022, ¶123.

The weight of the evidence shows that a POSA would have known that eculizumab is a humanized 5G1.1 antibody with an IgG2/IgG4 constant region, as Alexion confirmed during prosecution.

B. Dr. Casadevall's stated concerns over modifications to an antibody's constant region are not relevant for eculizumab.

Dr. Casadevall alleges that a POSA would have been concerned that modifying an antibody's constant region may affect the antibody's binding properties, thereby lessening the artisan's reasonable expectation of successfully making and using eculizumab. ALXN2022, ¶¶105-118, 225-234. But such concerns are moot here because eculizumab was *already known in the art to have an IgG2/IgG4 constant region* – i.e., a POSA would not have needed to modify or engineer the antibody from the disclosures taught in the art. Paper 2, 16-21;

AMG1002, ¶¶43-49; AMG1081, ¶¶19-25. As the Petition demonstrated, the combination of Bowdish and Evans or Evans and Mueller taught the complete amino acid sequence of eculizumab (including its IgG2/IgG4 constant region). Paper 2, 45-54, 62-71. Thus, Dr. Casadevall's portrayal of a POSA's endeavor to "modify" eculizumab into an IgG2/IgG4 antibody is unrealistic, since a POSA would have already known eculizumab *is* an IgG2/IgG4 antibody.

Even assuming arguendo that a POSA somehow thought eculizumab had an IgG4 constant region—which is not the case here—the artisan still would have had a reasonable expectation of successfully making and using the IgG2/IgG4 eculizumab antibody. AMG1081, ¶¶79-84, 94. As the Petition showed, antibodies with an IgG2/IgG4 constant region were known in the art years before March 15, 2007, and a POSA would have known that an IgG2/IgG4 constant region offered advantages such as reduced ability to elicit unwanted inflammatory events and lessened propensity to activate the complement system. Paper 2, 17; AMG1032, 11, 19, 28; AMG1031, 451; AMG1002, ¶¶47, 57. Further, as the Board noted, "Bell teaches that a variety of compounds containing the variable regions of a humanized 5G1.1 are useful to the treatment of PNH." Paper 15, 46; AMG1005, ¶[0012]. Thus, a POSA reading any of the combinations of references in Grounds 2-7 would have had a reason to make an IgG2/IgG4 antibody with a reasonable expectation of success. AMG1081, ¶¶68-84, 89-94.

As Dr. Balthasar explains, a POSA would have known from the art that references like Mueller II and Tacken disclosed comparable binding properties between two antibodies when one is modified to an IgG2/IgG4 antibody. AMG1081, ¶¶81-82; AMG1031, 448, Fig. 7; AMG1034, 1080. Other references in the art, such as Evans and Thomas, disclosed that 5G1.1 antibodies retain their function when changing isotype, or even when deleting the constant region altogether. AMG1081, ¶83; AMG1023, 1396; AMG1007, Example 12. Thus, contrary to Dr. Casadevall's testimony, a POSA would have had a reasonable expectation of successfully making and using a 5G1.1 antibody with an IgG2/IgG4 isotype because the art taught that changing to an IgG2/IgG4 constant region does not significantly impact the binding properties of the antibody. AMG1081, ¶¶81-84. Indeed, *none* of the examples Dr. Casadevall cites discloses testing *any* antibodies with an IgG2/IgG4 constant region. ALXN2022, ¶¶116, 118; AMG1077, 191:7-12, 192:6-12, 193:23-194:11, 196:16-197:7, 198:22-199:8, 200:13-202:11, 203:20-205:7, 208:10-209:18.

C. Alexion does not dispute that eculizumab's amino acid sequence was disclosed in the prior art.

The Petition showed that the complete amino acid sequence of eculizumab was disclosed in the combination of Bowdish and Evans (Grounds 4-5) or Evans and Mueller (Grounds 6-7). Paper 2, 45-51, 62-69. Coupled with Bell's disclosures of successfully treating PNH patients with a pharmaceutical composition

comprising eculizumab, and Wang's disclosures of stable formulations of eculizumab from 1-30 mg/ml, the combinations of Bell, Bowdish, and Evans (and Wang) (Grounds 4 and 5) and Bell, Evans, and Mueller (and Wang) (Grounds 6 and 7) rendered obvious claims 1-10. *Id.*

Alexion does not dispute that these combinations of references disclose the claimed sequences. AMG1081, ¶¶61-66, 87-88. Instead, Alexion argues that there would have been no *reason* to select and combine the sequences from Bowdish and Evans (or from Evans and Mueller), no *motivation* to make "a new, untested antibody," and no reasonable expectation that "such a new untested antibody" would be suitable for a pharmaceutical composition for treating PNH patients. Paper 22, 42-43, 58-59. Alexion's arguments fail because they are founded on a mischaracterization of the knowledge in the prior art regarding eculizumab. A POSA seeking to make eculizumab would not have endeavored to make a "new, untested antibody." On the contrary, the artisan would have endeavored to make the antibody that was already known, tested, and shown to be safe and effective in patients with PNH: eculizumab. AMG1081, ¶¶10-11, 68-72.

Alexion's argument that Bowdish "did not concern the development of anti-C5 antibodies at all" and has "nothing to do with C5 binding or treatment of PNH" also fails. Paper 22, 49; Paper 15, 45. A POSA would have considered Bowdish relevant art at least because (i) Bowdish is generally directed to therapeutic

antibodies; (ii) Bowdish discloses 5G1.1 as one of the scaffold antibodies used in the examples, which a POSA would have known refers to an anti-C5 antibody; and (iii) Bowdish cites and incorporates Evans[2] by reference. Paper 2, 16-17, 47-50; AMG1002, ¶¶139-144; AMG1006, ¶¶[0002], [0191]; AMG1081, ¶¶69-78. Indeed, the Board agreed with Amgen that Bowdish and Evans would have been pertinent to a POSA. Paper 15, 45. As Dr. Balthasar explains, a POSA would have understood that Bowdish's incorporation of Evans by reference for "[c]onstruction of 5G1.1" includes Evans's disclosures in Example 11 directed to *construction* of humanized 5G1.1 scFv fragments and is not limited to the preparation of the original mouse 5G1.1 antibody in Evans's Example 7 as Alexion argues. AMG1081, ¶¶76-77; AMG1006, ¶[0191]; AMG1007, Example 7 ("*Preparation* of Anti-C5 Monoclonal Antibodies"), Example 11 ("*Construction* and Expression of Recombinant mAbs").

Alexion relies on *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375 (Fed. Cir. 2019) to argue there is no reasonable expectation of success, but *OSI* fails to support Alexion's argument. Paper 22, 43. In *OSI*, the asserted references contained no data at all – no "clinical (human) data or preclinical (animal) data,"

[2] Bowdish cites and incorporates Evans as the '283 application, and there is no dispute that the '283 application "issued as Evans." Paper 22, 50; Paper 2, 5; Paper 15, 14.

nor any "in vitro (test tube) data" regarding the drug's (erlotinib) effect on treating non-small cell lung cancer. *OSI*, 939 F.3d at 1383. In contrast, Bell explicitly provided clinical data regarding eculizumab for treating PNH patients, and would have provided a POSA with a reasonable expectation of successfully practicing the method as claimed. AMG1005, ¶¶[0081]-[0096]; AMG1002, ¶¶143-144. Discussed above, even if a POSA did not understand that Bell's eculizumab was an IgG2/IgG4 isotype (which is contrary to the knowledge in the art), the artisan still would have had a reasonable expectation of successfully making and using the IgG2/IgG4 isotype antibody as claimed. AMG1081, ¶¶80-84.

Alexion also argues that "Evans did not disclose any full length humanized antibodies derived from '5G1.1'," but again the evidence shows otherwise. Paper 22, 50. Evans—an Alexion patent that, according to Alexion, "claims the Approved Product [Soliris®]"—explicitly described combining the humanized 5G1.1 scFv fragments "with constant region domains" that may be "constructed of a mixture of constant domains from IgGs of various subtypes" to "form *full length antibodies*." AMG1007, 45:24-33; AMG1009, 4; Paper 2, 64; AMG1002, ¶¶14, 173, 178. Dr. Casadevall agreed as much at deposition. AMG1077, 256:11-25.

Dr. Casadevall also confirmed that each of the heavy chain CDR3 sequences in Evans's humanized 5G1.1 scFv constructs consists of 13 amino acids, and Dr. Balthasar shows that those 13 amino acids are identical in each construct.

AMG1077, 238:12-252:22; AMG1081, ¶¶61-67; AMG1002, ¶136. Accordingly, as the Petition showed, a POSA would have had a reason to combine Bell, Bowdish, and Evans (and Wang) with a reasonable expectation of successfully practicing the method as claimed. Paper 2, 45-61.

Alexion also alleges that Mueller (another Alexion publication) would not have been pertinent to a POSA because Mueller "did not include any experiments or data on C5 binding or blocking C5 cleavage." Paper 22, 61. But as Dr. Balthasar explains, a POSA would have considered Mueller relevant art and would have had a reason to combine Evans and Mueller (along with Bell and Wang) because (i) Mueller discloses therapeutic humanized antibodies for use in humans; (ii) both Mueller and Evans (and Bell) use "5G1.1" nomenclature, which a POSA would have known refers to anti-C5 antibodies; and (iii) both Mueller and Evans use overlapping "CO12" nomenclature when referring to h5G1.1 constructs. AMG1081, ¶¶89-93; Paper 2, 16-17. As Dr. Casadevall admitted at deposition, he is not aware of "any references here that talk about 5G1.1 as something other than an anti-C5 antibody." AMG1077, 104:11-18. Thus, Mueller's lack of explicit data on C5 binding or blocking C5 cleavage would not have lessened a POSA's interest in Mueller.

Dr. Balthasar further explains that a POSA would have selected Evans's variable region and Mueller's constant region and combined the two because

Evans teaches that its humanized 5G1.1 scFv fragments can be converted into full-length antibodies and Mueller teaches that its hybrid IgG2/IgG4 constant regions are useful in humanized antibodies. AMG1002, ¶¶178-179; AMG1081, ¶¶89-93. That more than one combination of sequences from Evans and Mueller would have been obvious does not render the asserted combination of sequences any less obvious. *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

D. Alexion's arguments regarding the challenges to antibody formulations are unfounded.

Relying on Dr. Trout's testimony, Alexion argues that developing a pharmaceutical composition comprising an antibody is "an unpredictable art" and that the composition "would need to be tested to determine suitability for human use." Paper 22, 13 (citing ALXN2024, ¶¶41-56). Dr. Trout even testified that a POSA would need to develop an antibody formulation "from scratch." ALXN2024, ¶41. These arguments are inapposite for pharmaceutical compositions comprising eculizumab and stem from Dr. Trout wrongly assuming that no such formulations were known in the art. Indeed, when asked at deposition, Dr. Trout could not give a straight answer if he even knew what eculizumab is; admittedly, he had no opinion as to whether eculizumab's sequence was known in the art. AMG1078, 104:20-25, 105:14-19, 106:6-11, 108:1-18; ALXN2024, ¶¶62-63. Notwithstanding Dr. Trout's evasive testimony, a POSA seeking to make and use a

pharmaceutical composition comprising eculizumab would not have needed to "start from scratch" because such compositions had *already been disclosed in the art* and shown to *successfully treat PNH patients*. AMG1004, 553; AMG1005, ¶¶[0081]-[0096]; AMG1002, ¶¶35-42; AMG1081, ¶¶10, 40-50; ALXN2022, ¶176.

As Dr. Balthasar explains, and as Dr. Trout confirmed at deposition, neither Hillmen nor Bell disclosed any difficulties in formulating the pharmaceutical compositions of eculizumab, nor any issues associated with stability of the eculizumab antibody or of the pharmaceutical compositions comprising eculizumab. AMG1081, ¶¶43-44; AMG1078, 125:11-25, 133:15-135:6. Bell, Evans, and Mueller each expressly discloses that "[f]ormulations suitable for injection are found in Remington's Pharmaceutical Sciences," a reference Dr. Balthasar explains was well-known in the formulation art. AMG1005, ¶¶[0012], [0062]; AMG1007, 18:33-43; AMG1008, 24:24-35; AMG1081, ¶¶43-45. In fact, the '504 patent itself provides the same guidance on eculizumab formulations, along with a reference to Remington's Pharmaceutical Sciences. AMG1001, 16:45-58.[3] And Wang provided exemplary liquid eculizumab formulations that

[3] Dr. Balthasar also explains that Bowdish provides guidance on formulating eculizumab similar to Bell, Evans, Mueller, and the '504 patent. AMG1081, ¶¶43-45; AMG1006, ¶[00148].

were sufficiently stable for pharmaceutical use. AMG1002, ¶¶113-114; AMG1028, ¶¶[0171]-[0173], Fig. 10; AMG1081, ¶¶46-47.

E. Dr. Trout's stated concerns about risks of antibody aggregation are not pertinent to formulations for intravenous infusion.

Dr. Trout alleges that a POSA would have been concerned about "antibody stability issues related to the concentration of antibody formulations."[4] ALXN2024, ¶52. In particular, Dr. Trout states that a higher antibody concentration increases the risk of antibody aggregation and thus the risk of decreased formulation stability. *Id.* As Dr. Trout admits, however, "high antibody concentration" was desirable for *subcutaneous* injections due to the small volumes required. *Id.* But formulations for *intravenous* infusion do not have such high concentrations. AMG1081, ¶¶51-52; AMG1030, 692; AMG1078, 184:15-185:10. And Dr. Trout agreed that a range of antibody concentrations from 1 to 10 mg/ml—the relevant range for intravenous administration of a therapeutic antibody—is "not dramatically affected by adherence or aggregation losses." AMG1078, 181:18-182:4; AMG1030, 692. As Dr. Balthasar explains, a POSA would have been aware that stability only "bec[omes] a significant concern" when

[4] Notably, Dr. Trout confirms that none of the '504 patent claims require that the pharmaceutical compositions comprising eculizumab have any particular level of stability. AMG1001, claims; AMG1078, 169:18-170:9.

an antibody concentration is much higher than 10 mg/ml. AMG1081, ¶52; AMG1030, 692.

Given this, a POSA reading any of Hillmen, Bell, and Evans, which each disclosed *intravenous infusion*, would not have been concerned about the antibody aggregation and stability issues associated with subcutaneous formulations, rendering Dr. Trout's arguments moot. Paper 2, 32, 55; AMG1081, ¶¶51-53.

F. The claimed single-unit formulations would have been obvious.

The Petition showed that Bell disclosed administering eculizumab in a single-unit dosage form, and both Hillmen and Bell taught administering eculizumab in doses of 600 mg and 900 mg. Paper 2, 40-41, 57; AMG1002, ¶¶97-118. As Dr. Balthasar explained, given these teachings in the art, a POSA would have understood a 300 mg single unit dosage amount to be the most obvious, convenient, and predictable amount to make in order to administer the 600 mg and 900 mg doses of eculizumab taught in Hillmen and Bell. *Id*.

Alexion's and Dr. Trout's only response is that making a 300 mg single-unit dosage would be "inconvenien[t]" with a "greater possibility of provider error." Paper 22, 41; ALXN2024, ¶91. As Dr. Balthasar explains, however, there is always a possibility of provider error, no matter what the formulation; and having more than one strategy for developing a formulation in no way diminishes the efficiency and ease of the 300 mg single-unit dosage form as showed in the

Petition. AMG1081, ¶¶55-58. *Merck*, 874 F.2d at 807 (for obviousness, "all disclosures of the prior art, including unpreferred embodiments, must be considered.")

The Petition also showed that Wang disclosed stable eculizumab formulations with concentrations between 1 and 30 mg/ml, completely encompassing the '504 patent's claimed 10 mg/ml concentration in claim 6, and thereby contributing to the prima facie obviousness (Grounds 3, 5, 7). Paper 2, 41-45, 60-61, 71; AMG1028, Fig. 10, ¶¶[0170]-[0172]; AMG1002, ¶¶110-118; *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003).

Alexion argues that Wang's formulations were designed for nebulizers and were therefore not relevant to intravenous formulations, but this is simply not true. Paper 22, 38; ALXN2024, ¶81. Instead, as Dr. Balthasar explains, a POSA would have considered Wang's nebulizer formulations highly relevant for intravenous formulations because the art taught that nebulization formulations can be prepared from existing intravenous or other liquid formulations. AMG1081, ¶47; AMG1087, 3; AMG1086, 1305-1306. Thus, given Wang's teaching that eculizumab can be stably formulated for nebulization at a concentration of 1-30 mg/ml, a POSA would have had a reasonable expectation of success that eculizumab could be stably formulated at 10 mg/ml for intravenous infusion. Paper 2, 42-44; AMG1002, ¶113; AMG1081, ¶¶51-54.

G. Alexion fails to present any objective indicia weighing in favor of patentability.

Each of Alexion's objective indicia arguments fails to weigh in favor of patentability for multiple reasons.

1. Alexion fails to establish commercial success.

Alexion argues that the "antibody comprising SEQ ID NOs: 2 and 4" is responsible for its alleged commercial success. Paper 22, 64. However, "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). Because all of the limitations of the challenged claims, including eculizumab's IgG2/IgG4 constant region sequence, were known in the prior art, they cannot be pertinent to SOLRIS's commercial success. *Id.*

Further, neither Dr. Casadevall nor Mr. Bazarko provides any semblance of a commercial success analysis. ALXN2022, ¶¶280-282; ALXN2056, ¶¶4-9; AMG1077, 281:8-18; AMG1080, 25:19-28:13; AMG1088, ¶¶14-16, 24-43. Mr. Ivan Hofmann, an expert in economics and market analysis, explains that neither Dr. Casadevall nor Mr. Bazarko considered important aspects of a commercial success analysis such as the existence of a blocking patent, market share analysis, or Orphan Drug exclusivity benefits. AMG1088, ¶¶14-16, 24-43. Thus, Alexion's mere report of sales data is inadequate to establish commercial success, especially when the feature driving sales is disclosed in the prior art.

2. Alexion fails to establish a long-felt, unmet need.

Alexion also fails to establish a long-felt, unmet need, because any such need for a treatment for PNH was already met by the art. *Novartis AG v. Torrent Pharm.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017). The '504 patent discloses that the claimed methods of treatment improve "certain aspects of quality of life which are incurred in PNH patients." AMG1001, 6:46-50. As Dr. Casadevall admits, other treatments for PNH that provided patients with improved quality of life, e.g., blood transfusions, existed in the art long before March 15, 2007. AMG1077, 278:14-24. Additionally, Alexion's published clinical trials in Hillmen, Bell, Hill '05, and Hillmen '06 all disclosed successfully treating PNH patients with pharmaceutical compositions comprising eculizumab, thereby meeting any purported need before the '504 patent. *Novartis*, 853 F.3d at 1331; AMG1081, ¶¶96-98.

3. Alexion's evidence of industry praise fails to support patentability.

Alexion's evidence of industry praise amounts solely to two Prix Galien awards. Paper 22, 66. Alexion fails to show that any evidence of praise is connected to something not already in the prior art. *Kao*, 639 F.3d at 1068; AMG1081, ¶99. Further, when cross-examined on the subject of praise, Dr. Casadevall was unfamiliar with the Prix-Galien award and could not explain the criteria used to choose the award recipients. AMG1077, 285:2-13.

4. Alexion's copying arguments also fail.

It is well settled that evidence of copying gets very little weight in Hatch-Waxman litigation "because a showing of bioequivalence is required for FDA approval." *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013). The Board should apply a similar principle here because the statutory standard for regulatory approval of biosimilars requires that the biosimilar product be "highly similar to the reference product" with "no clinically meaningful differences … in terms of the safety, purity, and potency of the product." 42 U.S.C. §262(i)(2). Accordingly, any evidence of copying should get no weight.

IV. Conclusion

The Board should cancel the challenged claims as unpatentable.

Respectfully submitted,

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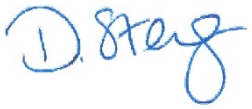

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CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

I certify that the Petitioner's Reply to Patent Owner Response contains 5,524 words as counted by the word-processing program used to generate this Reply. This total does not include the table of contents, certificate of service, or this certificate of word count.

Respectfully submitted,

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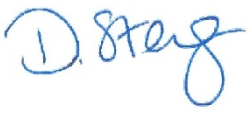

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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

The undersigned hereby certifies that the above-captioned "Petitioner's Reply to Patent Owner Response" was served in its entirety on February 14, 2020, upon the following parties via email:

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