UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2019-00741
U.S. Patent No. 9,732,149 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, 13; *see also,* ALXN2022, ¶¶100; AMG1081, ¶¶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, 50-51; Paper 22, 13.

Further, there is *no dispute* that the eculizumab antibody reported in Alexion's clinical trial publications did indeed possess the claimed amino acid sequences SEQ ID NOs. 2 and 4 of the '149 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, 29.

The primary issue of dispute in this IPR thus boils down to whether a POSA before March 15, 2007 would have known or been able to determine from the art, the amino acid sequence of eculizumab. Alexion's POR obscures the issues by asserting incorrect legal standards and mischaracterizing the knowledge in the prior art.

First, Alexion argues that Hillmen does not inherently anticipate claim 1 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, 32-33. 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 and Hill '05 "necessarily" include the claimed sequences of SEQ ID NOs: 2 and 4 is binding and dispositive, given that there was sufficient information in the prior art—including in Alexion's own

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

publications—that would have allowed a POSA to make and use eculizumab before March 15, 2007.. AMG1014, 767(¶6); Paper 22, 29; Paper 2, 28-30, 33-34.

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, 15-17, 25-26. 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, 15-16; AMG1002, ¶45; AMG1034, 1279.

Amgen's Petition showed by a preponderance of the evidence that claim 1is 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 claim 1 as unpatentable.

II. Alexion's admissions confirm that Hillmen and Hill '05 inherently anticipate claim 1.

Alexion admitted that the eculizumab Hillmen and Hill '05 each disclosed administering 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, 29 ("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.*, 32 ("today … it is known that the clinical studies underlying the Hillmen and Hill publications *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, 33 (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 and Hill '05's disclosures of

eculizumab, and the Petition showed that each reference is enabling in light of the general knowledge in the art. Paper 2, 28-30, 33-34.

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, 67.

Alexion's reliance on *Bayer* also misses the mark. Paper 22, 33. 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 and Hill '05 each discloses using *eculizumab*, not a chemical compound with an experimental code name. AMG1004, Abstract; AMG1047, 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, 13.

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, 21-22. 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, 24-34; *see also*, AMG1081, ¶¶37-40.

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, 32. Not so. The Petition points to other references solely to demonstrate the knowledge in the art showing that each of Hillmen's and Hill '05's disclosures fully enabled the claimed antibody. Paper 2, 28-31, 33-34.

III. Bowdish inherently anticipates claim 1.

Alexion's response to Ground 3 is essentially the same argument Alexion asserted in its Preliminary Response ("POPR," Paper 10), which the Board squarely rejected in its Institution Decision. Paper 15, 36-38. Alexion first attempts to cast doubt on the sufficiency of Bowdish's incorporation of Evans by reference, arguing that Bowdish incorporates the '283 application and not Evans, and that the incorporation is not effective to incorporate any specific material from Evans. Paper 22, 36-38. But as the Board explained in its Decision when rejecting this very argument, Bowdish does indeed incorporate Evans, and *all of* Evans is effectively part of Bowdish:

> *Bowdish incorporates Evans by reference* … which means that Evans's disclosure, in particular that portion describing the construction of a 5G1.1 antibody, is integrated from Evans into the Bowdish host document; *Bowdish makes clear that Evans is effectively part of Bowdish as if it were explicitly contained therein* … Petitioner is not "combining" Bowdish and Evans. Bowdish has already combined the two as an integrated document.

Paper 15, 38 (internal citations omitted); *see also, Paice LLC v. Ford Motor Co.*, 881 F.3d 894 (Fed. Cir. 2018).

Alexion's fallback position is that even if Bowdish does incorporate Evans by reference, the incorporation is limited only to Evans's disclosures related to the

parent *mouse* 5G1.1 antibody. Paper 22, 38. In particular, Alexion alleges that Bowdish's reference to "[c]onstruction of 5G1.1" in Evans specifically and only refers to the parent 5G1.1 mouse antibody. *Id.*, 38. Alexion's argument conveniently ignores the express description of the examples in Evans. AMG1081, ¶¶41-49. As Dr. Balthasar explains, a POSA would have understood that Evans's Example 11—which discloses the humanized 5G1.1 scFv constructs containing the native heavy chain CDR3 sequence from Bowdish's 5G1.1 scaffold antibody—is expressly entitled "*Construction* and Expression of Recombinant mAbs," and Evans begins the example by stating that "[r]ecombinant DNA *constructions* encoding the recombinant mAbs comprising the *5G1.1 CDRs* are prepared by conventional recombinant DNA methods…." AMG1007, 42:56-62; AMG1081, ¶46. Evans also discloses "*CDR sequences* that are *useful in the construction* of the *humanized antibodies* of the invention." AMG1007, 8:50-52.

By comparison, Evans's Example 7—which discloses generating the parent 5G1.1 mouse antibody—is entitled "*Preparation* of Anti-C5 Monoclonal Antibodies." AMG1007, 37:36. Here, Evans discloses that a mouse monoclonal antibody "was *prepared*" (not constructed) using the typical steps for generating a mouse monoclonal antibody: immunizing mice, isolating spleen cells, making hybridomas, and screening the hybridomas for the desired antibody activity. AMG1007, 37:36-39:30; AMG1081, ¶46. Thus, even if a POSA considered

Bowdish's incorporation statement to be limited to "construction of 5G1.1," the artisan would have understood this to refer to Evans's construction of the humanized 5G1.1 scFv constructs detailed in Example 11. AMG1081, ¶46.

Alexion's comparison of the amino acid sequences of the mouse 5G1.1 antibody and Bowdish's *humanized IgG2/IgG4* TPO-mimetic antibody sequence is a red herring. First, Alexion's expert Dr. Nussenzweig admitted he has no personal knowledge of *any* of the 5G1.1 sequencing work Alexion purportedly had done. AMG1079, 34:24-35:10, 36:4-61:23. And as Dr. Balthasar explains, it is no surprise—and frankly irrelevant—that the fully mouse 5G1.1 antibody has different amino acid sequences compared to a humanized, IgG2/IgG4 antibody. AMG1081, ¶44. This difference in sequence does not detract from a POSA's understanding that Bowdish's incorporation of Evans includes Evans's Example 11 disclosures. *Id.* Moreover, even if Bowdish's incorporation statement were limited to the mouse 5G1.1 antibody in Evans (which it is not), Evans discloses that the mouse 5G1.1 antibody has the *same heavy chain CDR3 sequence* as the humanized 5G1.1 scFv constructs. AMG1081, ¶¶42-43, 47; AMG1007, Fig. 19.

Alexion's argument that a POSA would not have known "the precise structure of Bowdish's 'scaffold' antibody" also fails. Paper 22, 45-47. As the Petition demonstrated, Bowdish discloses *the complete sequences of the heavy and light chains* of the recombinant TPO-mimetic antibody, and expressly states that

the TPO mimetic was "transplanted *into the heavy chain CDR3*" of the 5G1.1 scaffold antibody "to *replace the native CDR3*." AMG1006, ¶[0191]; AMG1002, ¶¶91-93. And Evans explicitly provides a specific heavy chain CDR3 sequence of the *same 13 amino acids* in *all* of the humanized 5G1.1 scFv constructs, as well as the parent 5G1.1 mouse antibody. AMG1007, Example 11 and Fig. 19; AMG1081, ¶¶42-44; AMG1077, 238:12-252:22. Thus, as Dr. Balthasar explains, there is no ambiguity about what sequence was removed from Bowdish's 5G1.1 scaffold antibody to be replaced with the TPO mimetic. AMG1081, ¶¶42-43.

Finally, Alexion's argument that Bowdish does not disclose "[a]n antibody that binds C5" was also squarely rejected in the Board's Decision on Institution. Paper 22, 48-50; Paper 15, 35-38. As the Board rightly noted, "Bowdish is clear that its starting antibody is the antibody with a structure as shown in its Figures 13A and 13B, but constructed as Evans taught to construct a 5G1.1 antibody, which Evans confirmed is an anti-C5 antibody." Paper 15, 38. And Dr. Casadevall admitted at deposition that 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; AMG1081, ¶¶16-18.

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

As the Petition showed, the claimed antibody would have been obvious in view of the asserted art in Grounds 4-5. Paper 2, 41-57; AMG1002, ¶¶104-137. 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, 13-26. 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, ¶¶45-46; AMG1081, ¶¶50, 72.

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, 13; ALXN2022, ¶102;

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, ¶45; Paper 2, 15-16. Alexion argues that Tacken is "ambiguous" and has "nothing to do with C5 binding," but those arguments fail. Paper 22, 26. 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, ¶45; AMG1081, ¶¶19-25; AMG1077, 134:25-135:5. Alexion's argument that Taken "has nothing to do with C5 binding" likewise fails because Tacken expressly discloses eculizumab and states that it "is specific for the human terminal complement protein C5." AMG1034, 1279. Tacken would have been pertinent to a POSA. AMG1081, ¶19.

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. Alexion attempts to distance itself from these admissions by arguing that they are "non-prior art statements" and "not related to the '149 patent." Paper 22, 58. 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, 17;

ALXN2022, ¶122; 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, 15-16; 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, ¶¶42-48; 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, ¶122.

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, ¶¶104-117.221-229. 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, 15-20; AMG1002, ¶¶42-48; 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, 41-57. 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 reason to make the IgG2/IgG4 eculizumab antibody, with a reasonable

expectation of success in so doing. AMG1081, ¶¶66-71, 79. 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, 15-16; AMG1032, 11, 19, 28; AMG1031, 451; AMG1002, ¶¶46, 55. Thus, a POSA reading any of the combinations of references in Grounds 4-5 would have had a reason to make an IgG2/IgG4 antibody with a reasonable expectation of success. AMG1081, ¶¶55-71, 74-79.

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, ¶¶68-69; AMG1031, 448, Fig. 7; AMG1034, 1280. 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, ¶¶70; 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, ¶¶68-

71. Indeed, *none* of the examples Dr. Casadevall cites discloses testing *any* antibodies with an IgG2/IgG4 constant region. ALXN2022, ¶¶115, 117; 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 (Ground 4) or Evans and Mueller (Ground 5). Paper 2, 41-57. Coupled with Bell's disclosures of successfully treating PNH patients with a pharmaceutical composition comprising eculizumab, the combinations of Bell, Bowdish, and Evans (Ground 4) and Evans and Mueller (Ground 5) rendered obvious claim 1. *Id.*

Alexion does not dispute that these combinations of references disclose the claimed sequences. AMG1081, ¶¶52-53, 73. 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 "[a]n antibody that binds C5." Paper 22, 51, 64. Alexion's arguments fail because they are founded on a mischaracterization of the knowledge in the prior art regarding eculizumab. A POSA would have had a reasonable expectation of

making an antibody that binds C5 because the combinations of references in Grounds 4 and 5 each taught *anti-C5 antibodies*. AMG1081, ¶¶10-11, 55-59.

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, 56; Paper 15, 37. 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, 15-16, 42-44; AMG1002, ¶¶114-119; AMG1006, ¶¶[0002], [0191]; AMG1081, ¶¶55-65. Indeed, the Board agreed with Amgen that Bowdish would have been pertinent to a POSA. Paper 15, 37-38. As discussed above and 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, ¶¶46-47, 63-64; AMG1006, ¶[0191]; AMG1007, Example 7

[2] Discussed in Section III, *supra*, Bowdish cites and incorporates Evans as the '283 application, and there is no dispute that the '283 application "issued as Evans." Paper 22, 57; Paper 2, 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, 62-63. In *OSI*, the asserted references contained no data at all – no "clinical (human) data or preclinical (animal) data," 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 identified eculizumab as "[t]he specific *anti-C5 antibody* used in the study" and Evans disclosed preparing different humanized *C5-binding antibodies* referred to as "5G1.1" antibodies. AMG1005, ¶[0082]; AMG1007, 19:47-49, 37:35-39:30, 40:31-45:4; Paper 2, 38, 44. Such disclosures would have provided a POSA with a reasonable expectation of successfully making an antibody that binds C5 as claimed. AMG1005, ¶¶[0081]-[0096]; AMG1002, ¶118. 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 reason to make the IgG2/IgG4 isotype antibody as claimed, with a reasonable expectation of success. AMG1081, ¶¶66-71.

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, 57. 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, 50; AMG1002, ¶¶14, 122, 124. 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, ¶¶52-54; AMG1002, ¶111. Accordingly, as the Petition showed, a POSA would have had a reason to combine Bell, Bowdish, and Evans with a reasonable expectation of successfully making the claimed antibody. Paper 2, 41-47.

Alexion's hindsight argument mischaracterizes the arguments in the Petition and Dr. Balthasar's declaration. Paper 22, 60-62; Paper 2, 53-54. Alexion attempts to portray Dr. Balthasar's testimony and figures in his declaration as using the '149 patent as a reference point for his obviousness analysis, but that is not the case at all. Dr. Balthasar provides the sequence alignments simply as a visual aid to demonstrate that the sequences disclosed in the references are the same as those

claimed in the '149 patent, not as something a POSA would have done to make the claimed antibody. *See e.g.*, AMG1002, ¶¶51-53.

Further, Alexion implies that the other antibody fragments disclosed in Evans somehow detract from the obvious combination of sequences discussed by Dr. Balthasar and presented in the Petition. Paper 22, 61-62. As the Petition explained, however, the only sequence missing from Bowdish's 5G1.1 scaffold antibody is the heavy chain CDR3 sequence, and *all* of the 5G1.1 antibody heavy chain variable regions in Evans contain *the same CDR3 sequence*. Paper 2, 38; AMG1002, ¶95. "That the [asserted prior art] discloses a multitude of effective combinations does not render any particular formulation less obvious." *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

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, 64-65. But as Dr. Balthasar explains, a POSA would have considered Mueller relevant art and would have had a reason to combine Evans and Mueller because (i) Mueller discloses therapeutic humanized antibodies for use in humans; (ii) both Mueller and Evans 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, ¶¶74-78; Paper 2,

14-15. 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, ¶122; AMG1081, ¶¶74-78. 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*, 874 F.2d at 807.

D. 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 claim 1, 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, ¶¶270-272; ALXN2056, ¶¶4-9; AMG1077, 281:8-18; AMG1080, 25:19-28:13; AMG1088, ¶¶14-16, 24-42. 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 blocking patents, market share analysis, or Orphan Drug exclusivity benefits. AMG1088, ¶¶14-16-24-42. 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 '149 patent states that the disclosures relate to "improving certain aspects of quality of life which are incurred in PNH patients." AMG1001, 6:51-55. 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 eculizumab, thereby meeting any purported need before the '149 patent. *Novartis*, 853 F.3d at 1331; AMG1081, ¶¶80-82.

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, 69. 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, ¶83. 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

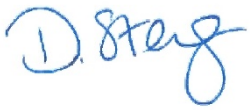
product." 42 U.S.C. §262(i)(2). Accordingly, any evidence of copying should get no weight.

V. Conclusion

The Board should cancel the challenged claim as unpatentable.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Date: February 14, 2020
1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

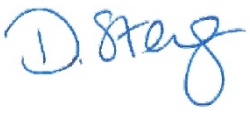
Deborah A. Sterling, Ph.D.
Registration No. 62,732
Lead Attorney for Petitioner

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

I certify that the Petitioner's Reply to Patent Owner Response contains 5,405 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,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Date: February 14, 2020
1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

Deborah A. Sterling, Ph.D.
Registration No. 62,732
Lead Attorney for Petitioner

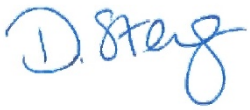
CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

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:

Gerald J. Flattmann, Jr.
Vanessa Y. Yen
Evan D. Diamond
KING & SPALDING LLP
1185 Avenue of the Americas
New York, NY 10036
(212) 556-2157
gflattmann@kslaw.com
vyen@kslaw.com
ediamond@kslaw.com
jevans@kslaw.com

Lori A. Gordon
KING & SPALDING LLP
1700 Pennsylvania Ave NW
Washington, D.C. 20006
(202) 737-0500 (reception)
lgordon@kslaw.com

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Date: February 14, 2020
1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

Deborah A. Sterling, Ph.D.
Registration No. 62,732
Lead Attorney for Petitioner

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