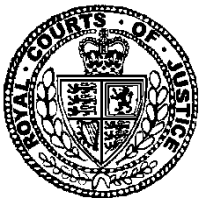


Neutral Citation Number: [2025] EWHC 1240 (Pat)
Case No: HP-2024-000020
HP-2024-000021

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES
INTELLECTUAL PROPERTY LIST (ChD)
PATENTS COURT

The Rolls Building
7 Rolls Buildings
Fetter Lane
London EC4A 1NL
20 May 2025

Before:

MR. JUSTICE MEADE

Between:

HP-2024-000020

SAMSUNG BIOEPIS UK LIMITED **Claimant**

- and –

ALEXION PHARMACEUTICALS, INC. **Defendant**

And Between:

HP-2024-000021

(1) ALEXION PHARMACEUTICALS, INC. **Claimants**
(2) ALEXION PHARMA INTERNATIONAL OPERATIONS LIMITED

- and -

(1) AMGEN LIMITED **Defendants**
(2) SAMSUNG BIOEPIS UKLIMITED

- -

Hearing dates: 18-21 and 26-27 March 2025

- -

JUDGMENT

MR TOM MOODY-STUART KC AND MR JEREMY HEALD (instructed by **Freshfields Bruckhaus Deringer LLP**) for **Alexion**

MR ANDREW WAUGH KC AND MS KATHERINE MOGGRIDGE (instructed by **Osborne Clarke LLP**) for **Amgen**

MR JUSTIN TURNER KC AND MR JAMES WHYTE (instructed by **Simmons & Simmons LLP**) for **Samsung Bioepis**

- -

Remote hand-down: This judgment will be handed down remotely by circulation to the parties or their representatives by email and release to The National Archives. A copy of the judgment in final form as handed down should be available on The National Archives website shortly thereafter but can otherwise be obtained on request by email to the Judicial Office (press.enquiries@judiciary.uk).

Mr Justice Meade:

INTRODUCTION

1. This is the trial of two actions, HP-2024-000020 and HP-2024-000021 concerning European Patent (UK) No. 3 167 888 B1 ("the Patent").

2. At trial:

   i) Tom Moody-Stuart KC appeared for the two Alexion entities (together, "Alexion"), leading Jeremy Heald;

   ii) Justin Turner KC represented Samsung Bioepis UK Limited ("SB"), leading James Whyte;

   iii) Andrew Waugh KC appeared for Amgen Limited ("Amgen"), leading Katherine Moggridge.

3. The litigation relates to a successful antibody drug called eculizumab, originally developed by Alexion, which is used in particular for the treatment of a rare but serious condition called paroxysmal nocturnal haemoglobinuria, known as "PNH".

4. I refer to SB and Amgen jointly in this judgment as "the Defendants". They each want to sell a biosimilar eculizumab. There is in general no need to distinguish between their positions, except that it is only SB that runs the arguments on judicial estoppel and approbation and reprobation. Although their products, which Alexion alleges infringe the Patent, have been developed independently and will not be identical, the infringement issues that they raise are the same.

5. SB and Amgen had separate solicitors.

6. Initially, eculizumab was protected by a patent family which I will refer to generically as the "Evans" family, having a priority date of 2 May 1994. Patents from this family were directed to the binding regions of therapeutic antibodies (what this means is explained below) and covered eculizumab but did not specifically disclose it.

7. In Europe, the relevant Evans patent was EP 0 758 904, which was the basic patent allowing an SPC to be obtained covering eculizumab. Protection under the SPC ran all the way until 2020, and eculizumab had the full five years of added protection (the Defendants criticise that having happened, but I agree with Alexion that it was simply the consequence of a more lenient legal test for SPC validity than applied later).

8. There was also another related drug called pexelizumab, which had the same binding regions as eculizumab in a different antibody format, and was also covered by the Evans family, but it was unsuccessful in the clinic.

9. In 1999, Alexion submitted an entry to the Chemical Abstracts Service ("CAS") in relation to eculizumab.

10. However, the sequence of eculizumab submitted to CAS was erroneous. The precise nature of the sequence error does not matter, but it was a major one.

11. The purpose of the CAS submission was to get an International Non-proprietary Name ("INN") for eculizumab, and it was published as such in an INN Proposed List in 2002 and a Recommended List in 2003.

12. Alexion later realised the CAS sequence was wrong, and submitted a correction in 2009.

13. Clinical work went on in relation to eculizumab, and there were a number of important papers, including one referred to as Hillmen 2004 and another referred to as Hillmen 2006, both in the New England Journal of Medicine. Hillmen 2006 describes a clinical trial called TRIUMPH.

14. Alexion continued to seek protection for eculizumab in various forms and various patent filings. The Patent is one of a family with a filing date of 15 March 2007, claiming a priority date of 15 March 2006.

15. The specification of the Patent largely describes the TRIUMPH trial and as filed the claims were directed in a variety of ways to the use of eculizumab in accordance (at varying levels of detail) with the regimen used in the trial, but for reasons that it is unnecessary to describe it turned out that the claim to the priority date of 15 March 2006 could not be maintained. That meant that Hillmen 2006 was prior art (indeed it is accepted to be common general knowledge ("CGK")) and the originally intended claims would not be possible.

16. However, Alexion, having appreciated that the original CAS filing was wrong, changed strategy and sought protection for eculizumab as such, on the basis that it had never in fact formed part of the state of the art.

17. Against this already rather extraordinary background, a further error emerges: the light chain sequence (again, explained below) by which the antibody the subject of the Patent claims is partly characterised, referred to as "SEQ ID NO: 4", is not exactly eculizumab. It has 22 extra amino acids, which are a leader sequence.

18. In an attempt to deal with this, in prosecution Alexion applied to amend the claims so as to define a light chain not having the additional 22 amino acids. This was not allowed by the EPO, ultimately by a decision of the TBA of 21 September 2024 (T1515/20, "the TBA decision"), because of added matter objections. So the Patent was granted, on 1 May 2024, with claims defined in terms of the original SEQ ID NO: 4, having the 22 additional amino acids.

19. The Defendants' products' light chains will not have the additional 22 amino acids but rather the exact same sequence as eculizumab.

20. Separately, Alexion has over the years sought other patent protection relating to eculizumab, and it has been in something of a cleft stick because in some patent filings it has wanted, when meeting insufficiency challenges, to say that eculizumab *was* part of the state of the art by virtue of the CAS filing and/or the Evans family, while in other proceedings, including this one, it has wanted to say that eculizumab was *not* part of the state of the art, for novelty or inventive step reasons.

21. The Defendants (as mentioned above, SB more than Amgen) criticise this behaviour under a number of legal headings. Their cases have narrowed from a rather diffuse and broad scope, including for example statements made to the USPTO. The high water mark is a patent family with a priority date in 2004 in which Alexion positively relied (in an EPO filing of 20 December 2013 for patent EP 1 720 571) on the original CAS sequence for enablement, even after it had realised that the sequence was wrong and had corrected it. As best one can tell (from the Opposition Division's revised preliminary opinion of 18 February 2014) this incorrect submission is what satisfied the EPO that there was not an enablement problem, i.e. it was necessary to maintaining validity. In fact the '571 Patent was eventually revoked in 2018 but Alexion had the benefit of its existence in the meantime, albeit that what commercial effect that had cannot be known.

22. Alexion points out that it is not alleged that any of its errors were other than innocent. That of course does not mean that the Defendants positively accept that they were mere innocent slips, but in any case I am not dealing with a situation where the Defendants allege any positive ill-intent on Alexion's part and I am not called on to make any findings about the subjective state of mind of its people.

23. With this somewhat high-level description of the background, which is necessarily simplified for brevity at this stage, I can describe the issues and the ways in which they interact.

24. On infringement, Alexion says that the Defendants' products infringe the claims of the Patent on a purposive construction. It says that the skilled reader of the Patent would realise that the 22 additional amino acids do not make sense as part of the mature protein, being a leader sequence that would inevitably be cleaved off in normal production, and would understand the claim as really requiring a light chain without them. This case is advanced only as one of purposive construction; equivalence is not relied on.

25. The Defendants on the other hand say that the Patent's claims are limited to what they literally say and that the 22 amino acids are required, on both a literal and purposive construction.

26. Alexion has accepted that if the Defendants are right about claim construction then the Patent is invalid. It says that this is a pragmatic concession because if there is no infringement then the claims are worthless.

27. As part of their claim construction arguments, the Defendants rely, although they do not say it is essential to their case, on the prosecution file history. They say resort to it is justified either to resolve an ambiguity in the claims (although their primary case is that they are not ambiguous and bear the meaning for which the Defendants contend) or on the grounds of public policy, relying on Alexion's unsuccessful attempts to get claims that would have been literally infringed and which did not require the 22 amino acids.

28. A major feature of the claim construction arguments is that the Patent specification says that eculizumab was part of the state of the art, in particular by reference to the Evans patent family. The Defendants say that the skilled reader would not think the claims would read onto the acknowledged prior art. Alexion

says that the recognition in the specification that eculizumab was known is mistaken, and that the skilled person would realise that, if or when they went back to Evans.

29. If Alexion is right about claim construction, so that the claims cover eculizumab as such, then the Defendants do not dispute that their products fall within the claims. But they say that the claims are then invalid on a number of bases: that they are anticipated or obvious over certain prior art (all from Alexion and including Evans), and that they are insufficient for lack of plausibility and/or *Agrevo* obviousness.

30. As I have already mentioned, the Defendants also rely on the unusual history of the patent protection of eculizumab and say that Alexion should lose even if the Patent would be infringed and valid on the attacks I have already mentioned:

    i) SB say that Alexion is prevented by a judicial estoppel or by the doctrine against approbation and reprobation from denying that eculizumab was part of the prior art, so the Patent should be revoked as if it was. This attack is only pleaded and made by Samsung Bioepis and was argued by Mr Turner, although since its result would be the revocation of the Patent it would also save Amgen.

    ii) SB and Amgen both say that Alexion's claim in these proceedings is an abuse of process by virtue of its repeated changes of position as to whether either Evans or the CAS sequence made eculizumab part of the state of the art. So, they say, the claim should be dismissed even if it would otherwise succeed and even if the Patent is valid; indeed even, as I understood it, if the judicial estoppel and approbation/reprobation arguments fail.

CASE MANAGEMENT

31. I expedited the trial by my Order of 6 June 2024 at the application of SB because of concerns they raised about Alexion making communications about the Patent to potential customers.

32. My Order did not require the Defendants to share leading Counsel but it did require that if they had separate leading Counsel they could not both make submissions on the same subject. This was implemented at trial by a rather complex division of labour between Mr Turner and Mr Waugh, which was not a clean one because they both referred to the same facts about patent prosecution conduct, but in the end it worked without any real difficulty.

33. The only oral advocacy conducted by junior Counsel was that Mr Whyte dealt with some of the evidence in chief and with an objection that arose in the course of the cross-examination of Mr Buss. Although this might at first glance seem like an under-use of junior Counsel in the context of the Patents Court Guide and current practice, it was in fact perfectly appropriate given that on the Defendants' side there were already two leading Counsel and the Defendants no doubt quite fairly (even if it was a bit messy) wanted some parity of involvement in the presentation, and the issues were all so tightly integrated that on Alexion's side it

was appropriate to use only one advocate. I mention all this only to make clear that this case does not represent a retreat from the Patents Court's general policy of encouraging the use of junior advocates at trial.

34. Although SB initiated the first numbered action, at trial Alexion took on the role of Claimant and opened the case, since infringement was live.

THE ISSUES

35. The technical issues are:

    i) The identity and characteristics of the skilled team;

    ii) The scope of the CGK;

    iii) Construction of the claims including reliance on the file history;

    iv) Anticipation by US application 2003/0232972 A1 ("Bowdish") in combination with US application 08/487,283 ("Evans" – it should be noted that the Evans application itself is of bad quality and the parties agreed to use US Patent 6,355,245 for convenience instead, on the basis that the contents are identical);

    v) Obviousness over:

        a) Bowdish in combination with Evans, either with or without (but primarily with) another non-CGK publication, an article entitled "Inhibition of complement activity by humanized anti-C5 antibody and single-Chain Fv", Molecular Immunology Vol. 33 No. 17/18, 1996, ("Thomas") that would, it was said, be found by routine research from the CGK starting point of Hillmen 2006; or

        b) An article entitled "Effective induction of naïve and recall T-cell responses by targeting antigen to human dendritic cells via a humanized anti-DC-SIGN antibody", by Tacken and others in Blood, volume 106 number 4, 15 August 2005 ("Tacken") in combination with an article entitled "Humanized porcine VCAM-specific monoclonal antibodies with chimeric IgG2/G4 constant regions block human leukocyte binding to porcine endothelial cells" by Mueller and others, Molecular Immunology, Vol. 34, No. 6, 1997 ("Mueller") and Thomas.

    vi) Insufficiency or lack of technical contribution/*Agrevo* obviousness.

36. The "Non-technical" issues are:

    i) Judicial estoppel;

    ii) Approbation and reprobation;

    iii) Abuse of process.

THE WITNESSES

37. Alexion called one expert, and the Defendants, two. They were:

    i) An antibody engineer (both sides);

    ii) A clinician (the Defendants only).

38. No fact witnesses were called.

Alexion's expert, Prof Nimmerjahn

39. Professor Falk Nimmerjahn is currently the Director of the Division of Genetics (Department of Biology) at the Friedrich-Alexander-Universität Erlangen-Nürnberg ("FAU"). He has held this position since 2010 and became the Head of the Department of Biology at FAU in 2017. He was also appointed the Vice Dean for Research (Faculty of Natural Sciences) in 2019 at FAU.

40. Professor Nimmerjahn holds a diploma in Biology and obtained his doctorate in Immunology, which investigated the mechanism of endogenous MHC II – restricted antigen presentation at the Ludwig-Maximillians-University in Munich. Between 2004 and 2007, he worked as a postdoctoral researcher in the Laboratory of Molecular Genetics and Immunology at the Rockefeller University, New York. That research focused on how different antibodies mediate their activity, how antibody glycosylation interacts with Fcγ receptors, and which types of receptors were useful for this, with a view to optimising existing antibodies. He also has numerous publications and has authored a chapter in the 2nd ed of Molecular Biology of B cells. He is also a named inventor on many patents and patent applications.

41. The Defendants said that Prof Nimmerjahn was an Fc receptor specialist with at most limited experience relevant to therapeutic antibody development. I agree, and it is a point of contrast with Mr Buss who had more relevant practical experience, but it is not a personal criticism of Prof Nimmerjahn.

42. The Defendants also made some specific criticisms of Prof Nimmerjahn other than in relation to his experience.

43. The two main ones were that he had adopted untenable positions in relation to paragraphs [0191] and [0192] of Bowdish in saying that 5G1.1 was or might be murine and that the "parental" control was or might be murine. I deal with the substance of these issues below, but in relation to Prof Nimmerjahn's credibility I will say now that the criticisms do not persuade me that he was not being honest in what he said. One conclusion I reach below is that Bowdish is not very clear in its disclosure about this part of its work, which would make it hard indeed to say that Prof Nimmerjahn's views could be seen to be so obviously wrong that his credibility was affected.

44. A similar point was made about his evidence on the "3º" control in figure 14 of Bowdish. Since it was common ground that that was unclear I cannot see any

basis for saying that Prof Nimmerjahn was obviously wrong, or even just inconsistent, enough to undermine his credibility.

45. Even had I thought that Prof Nimmerjahn had been clearly and distinctly wrong about e.g. the details of Bowdish that would not necessarily reflect on his integrity. The disclosure is complicated and messy and mistakes happen.

46. At a more general level, I found Prof Nimmerjahn to be a very good and fair explainer of the technology and as clear and precise in his explanations as the subject matter allowed, given that some of the key documents are not completely clear. His demeanour in the witness box was excellent. Where I have preferred the views of Mr Buss that is not a comment on Prof Nimmerjahn's credibility or integrity, but mainly because of Mr Buss's greater practical experience.

Mr Buss, the Defendants' antibody engineering expert

47. Mr Timothy Buss has extensive experience in the field of antibody engineering, with a focus on antibody design, humanisation and expression. He is the current Head of Antibody Engineering at the Proteogenomics Research Institute for Systems Medicine ("PRISM") in La Jolla, California and has held this position since 2019.

48. Mr Buss obtained a Higher National Certificate in Applied Biology from the Cambridgeshire College of Arts & Technology in the UK in 1986. Mr Buss has held various positions in the antibody industry. Specifically, he worked at the Cambridge Centre for Protein Engineering from 1991 to 1993 under Sir Gregory Winter. That lab was responsible for the first ever antibody humanisation and the first humanisation of a therapeutic antibody. From 1993-2002, Mr Buss worked at the Fred Hutchinson Cancer Research Center as a scientist working on antibody engineering. Between 2002 and 2008 he worked at the Sidney Kimmel Cancer Center in San Diego, California as an antibody engineer, making and adapting antibodies targeting tumour markers. From 2008 to 2015, Mr Buss worked for Ambrx, Inc., as a Senior Scientist, and was responsible for antibody generation and development. Between 2015 and 2019, Mr Buss worked on a number of projects as a consultant, advising on antibody research.

49. Mr Buss has published several articles in connection with his research on antibody design, engineering and use, as well as being a named inventor on several patents and patent applications in the field of antibody engineering.

50. Alexion made no personal criticism of Mr Buss but said that the way he was instructed had caused problems with hindsight. I analyse this below and conclude that there was a serious problem with hindsight in relation to the Bowdish + Evans attack, and some hindsight in relation to the Tacken + Mueller + Thomas attack. But I conclude that the latter did not materially make a difference and that Mr Buss' overall evidence was not to be rejected as a result of these difficulties.

51. Not that it really matters, but I doubt if the hindsight problems that arose were as a result of the way in which Mr Buss was instructed as such. I am sure he was properly told to avoid hindsight and tried to do so. Rather, I think the problem was the intricacy of the Bowdish + Evans attack, its interaction with Thomas, the

crossover with the Tacken attack in relation to Thomas, and the fact that all the relevant publications were from Alexion. Anyone could slip into momentarily feeding prior art from one attack to the other. In a nutshell, the Bowdish + Evans attack was so fiddly that its very nature caused these problems.

52. Aside from the hindsight issues, Mr Buss was an excellent witness: clear and precise in his oral evidence and with a practical and realistic approach.

Prof Mehta, the Defendants' clinician expert

53. Professor Atul Mehta is a self-employed consultant haematologist and physician, focusing on general haematology and coagulation. He has been self-employed since 2019. He obtained his First-Class Honours BA from Cambridge University and also completed his medical degree there. He became a member of the Royal College of Physicians in 1980 and the Royal College of Pathologists in 1984. He completed his MD at Imperial College with his thesis titled, "Mitochondrial DNA and Chloramphenicol-induced Aplastic Anemia".

54. Professor Mehta has previously held consultant positions in various NHS hospitals and has experience across both malignant and non-malignant haematology. His academic work involved the study and treatment of rare metabolic and haematological disorders. He was appointed as a consultant haematologist at the Royal Free Hospital in 1986 and remained there, employed by the NHS, until his retirement in 2019. During this period, he also held consultant positions at University College London Hospitals, St John and St Elizabeth's Hospital, and at the Wellington Hospital.

55. Prof Mehta had a limited role to play and his oral evidence was correspondingly brief. The challenges to him were really limited to exploring the instructions that the skilled clinician might give to the antibody engineer. It was a consistent theme of Alexion's case that the skilled clinician's notional instructions were taken to be the precise recreation of eculizumab, nothing more and nothing less. That is however not a fair characterisation of the Defendants' case or of Prof Mehta's evidence, as I consider further below. In any event, there is nothing in the point that could amount to a personal criticism of Prof Mehta whose authoritative knowledge was obvious and whose demeanour and manner of expression were ideal.

THE SKILLED PERSON OR TEAM

56. I have considered the authorities on this issue in a number of recent judgments and there was no real disagreement between the parties as to the principles, which are usefully identified in *Illumina v Latvia* [2021] EWHC 57 (Pat), save possibly in relation to the point arising from *Conversant v Apple* [2019] EWHC 3266 (Pat) which I address below.

57. The parties' rival positions were:

    i) Alexion said that "the skilled addressee is either an antibody engineer with a good understanding of immunology working on or with an interest in

complement-mediated disease or a team including an antibody engineer without such an understanding and another person with a good understanding of immunology. The skilled person or team did not include a clinician … or have a specific focus on PNH."

ii) The Defendants said the skilled team would include an antibody engineer and a skilled clinician who "would likely be employed by, or working as a consultant to, a bio-pharma company."

58. I will go on below to identify the skilled person or team in accordance with these principles. For the reasons I will give, I agree with the Defendants. But at the outset I should say that the dispute is a rather pointless one because what it really goes to is whether eculizumab as a treatment for PNH was CGK. Alexion says not, and the reasons for this are to do mainly with the obviousness arguments. The reason the dispute is pointless is because Alexion accepts that it was CGK even for its skilled person that there was a pressing need for an effective treatment approach for PNH. It makes no sense that that could be CGK without it being CGK that eculizumab was an available treatment and Counsel for Alexion presented no argument about why it could make sense. So whatever the nature of the skilled person or team eculizumab as an effective treatment for PNH would be CGK.

59. However, as I say I will decide the issue.

60. First I must consider the problem the Patent solves. This is a somewhat unusual situation because of the mismatch between the specification which is so heavily concerned with the TRIUMPH clinical trial, and the claims, which are to an antibody binding C5 as such, or a pharmaceutical composition (for claim 2). But I do not think in the end that this is a problem. The practical utility of the antibody claimed as presented by the specification is to bind C5 and thereby treat disease, including PNH. The fact that the claims would be infringed by other uses does not undermine this, and the therapeutic focus is in any event justified by claim 2.

61. Alexion rather ducked this question, focusing instead on attacking the way that the Defendants used the skilled person to set up their obviousness cases. They said that the Defendants were setting up the skilled team as one whose sole mission was to obtain eculizumab. I disagree that that was the Defendants' approach but in any case it was rather a hole in Alexion's position that it did not have a clear conception of the problem that the Patent aims to solve. Perhaps the closest it came was that the purpose of the skilled person was "developing and evaluating C5-specific antibody products for use in a pharmaceutical composition." I fail to see how that purpose could be progressed without a clinical perspective, for example so that an understanding of the pathology of the disease could be factored in.

62. Second, I must have regard to real skilled teams. Here, the Defendants had the clear advantage that Mr Buss had worked in real teams developing therapeutic antibodies and said that a clinician was always involved. By contrast, Prof Nimmerjahn did not have experience developing therapeutic antibodies, let alone ones that that had reached the clinic. He did have some experience in academia

in relation to therapeutic antibodies, but clinicians had been closely involved in that work.

63. Third, I have to consider what "established field" there was. There clearly was an established field of development of antibody drugs, and in that field there were real teams including clinicians as I have just described. I also think there was a sub-field interested in complement-mediated disease, and indeed Alexion's formulation of the skilled team more or less accepted that. I agree with Alexion that there was no established field of precisely emulating eculizumab, but again that contention was not about identifying the skilled person but about attacking the Defendants' obviousness case.

64. Fourth, I have to exercise a value judgment to some extent; making the skilled team too specific risks loading the obviousness analysis against the patentee while make it too general risks diluting the CGK. It would be unfair to Alexion to define the skilled team as being one dedicated specifically to replicating eculizumab, but that is not what I am deciding and not what the Defendants argued.

65. Lastly, I have to address Alexion's point based on *Conversant*. In that case, Birss J (as he then was) held that the skilled person would not be someone from the PDA field, at least in part because an amendment had excluded PDAs from the claims. Alexion pointed to the fact that the Patent had moved away from its "Items" (see below) specific to therapy and PNH in particular. But there is no valid analogy to *Conversant*. There, the claims had been *narrowed* to *exclude* something specific. Here, the claims are *broader* than the "Items". They still cover the claimed antibodies when used to treat PNH and that is the utility discussed in the Patent's specification.

66. So I agree with the Defendants on the skilled team. For the avoidance of doubt, that does not mean the skilled team would have an exclusive focus on PNH, or on eculizumab, or on replicating eculizumab. But PNH would be among the team's interests as a complement-mediated disease, and eculizumab would be within their wider scope of interest too. I refer below usually to the "skilled person" rather than "skilled team" and I do so because after the clinician had given initial direction to the project the work would essentially be in the hands of the antibody engineer, so it is more natural to refer to "person" in relation to those parts of the task. It should be noted that the ASCGK refers to the "Skilled Antibody Engineer". This expression was the choice of the parties, I assume partly as a neutral compromise. I have not tried to edit it out but it is not of material significance.

THE COMMON GENERAL KNOWLEDGE

67. In keeping with current practice in the Patents Court, there was a joint document which identified the CGK that was agreed (the "ASCGK") and another identifying what was in dispute. The initial document listing what was in dispute was much too long because it cut and pasted a lot of text concerning the disputed points. This is not a helpful way to proceed since it does not give the Court a

usable checklist, and parties will please in future work to come up with a concise list of propositions/items of information whose CGK status is in dispute.

68. Similarly, on the clinical CGK, where the Defendants had a separate expert but Alexion did not, I was provided with a marked-up version of Prof Mehta's report to show the agreed and disputed CGK. This is not what is required and there was no reason why the parties could not have done the usual and helpful job of preparing a summary of the agreed CGK and a list of disputed points.

69. The ASCGK was also very long and much of it was not relevant (the basics of DNA, for example). At my request the parties helpfully prepared a further version which highlighted the material said actually to matter to the issues, but I would encourage parties to do that job before trial as part of the preparation of the ASCGK in future. Many of the disputed points of CGK also turned out not to matter, although I acknowledge that parties are often uncertain of this until they see how things pan out at trial.

70. There was no general dispute about the law applicable to CGK. To be CGK, something must be generally known and accepted as a good basis for further action. It should be noted however, and I have already mentioned, that an important step in the obviousness attack over Bowdish with Evans involved the further addition of Thomas, which was not CGK, but which, it was said, would be found by routine research. I deal with this further below.

Agreed CGK

Proteins and Cellular Protein Synthesis

71. Amino acids are simple, small, naturally-occurring organic molecules sharing the same overall structure. They consist of an amino group (NH_2), a carboxylic acid group (COOH), a hydrogen atom (H) and a side chain group all attached to a central carbon atom (the alpha carbon). It is in the nature of the side chain that amino acids differ one from another, and it is upon these side chains that the various properties of the amino acids depend.

72. There are 20 common naturally-occurring amino acids, each of which is referred to by a three-letter abbreviation or code and a one-letter code, as follows:

Amino Acid	1-Letter Code	3-Letter Code
Alanine	A	Ala
Cysteine	C	Cys
Aspartic acid	D	Asp
Glutamic acid	E	Glu
Phenylalanine	F	Phe
Glycine	G	Gly
Histidine	H	His
Isoleucine	I	Ile
Lysine	K	Lys
Leucine	L	Leu
Methionine	M	Met
Asparagine	N	Asn

Proline	P	Pro
Glutamine	Q	Gln
Arginine	R	Arg
Serine	S	Ser
Threonine	T	Thr
Valine	V	Val
Tryptophan	W	Trp
Tyrosine	Y	Tyr

73. In the construction of proteins, each amino acid is joined to the next one by a peptide bond. A short chain of amino acids is referred to as a "peptide" and a long chain as a "polypeptide".

Proteins

74. Proteins are relatively large, complex, naturally-occurring organic molecules made of polypeptide chains. Most of the basic building blocks of cells, and many other important chemicals in nature, are proteins.

75. The structure of a protein can be considered at several levels. The primary structure is the linear sequence of amino acids. The secondary structure can be described as the physical appearance of individual sections (or segments) of the linear chain that arrange themselves in a particular way. The elements of secondary structure further fold upon themselves to create the tertiary structure which packs together the secondary structures and the amino acid side chains into stable structures known as domains.

76. A protein may consist of a single domain or may have multiple domains packed together into the complete protein structure.

Nucleic acids

77. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are large, complex, naturally-occurring organic molecules. These encode the information which is contained in an organism's genes.

78. Like proteins, nucleic acids are polymers composed of smaller units. In the case of DNA and RNA, the component units are relatively small, simple naturally-occurring organic molecules called nucleotides. One form of RNA is messenger RNA ("mRNA").

The genetic code

79. The correspondence between the nucleotide sequence of the mRNA and the amino acid sequence of the polypeptide chain is given by the genetic code. The bases are read in groups of three, and each triplet, or codon, codes for one specific amino acid. Because there are 64 (4^3) triplets, but only 20 amino acids, in most cases more than one codon is used to code for any particular amino acid. The genetic code is conveniently shown in the form of the table below:

THE GENETIC CODE

First Position (5' end)	*Second Position*				*Third Position (3' end)*
	U	C	A	G	
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	STOP	STOP	A
	Leu	Ser	STOP	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Genetic engineering

80. Manipulation of the nucleotide sequence in an organism's genes can alter the proteins that are produced by the nucleic acid. This is referred to as "genetic engineering". To enable such manipulation, small molecules known as vectors are used. A vector is a DNA molecule capable of directing its own replication in a host cell. Plasmids (double-stranded self-replicating DNA molecules) and bacteriophages are frequently used vectors. A vector can be used to "clone" DNA of interest by insertion of the DNA into the vector sequence. The insert is replicated and multiplied by the host cell as part of the vector. In this way the investigator can generate identical copies (clones) of the DNA on demand for further analysis and manipulation. Such DNA is often referred to as "recombinant" DNA.

Recombinant production of proteins

81. Proteins that result from the expression of recombinant DNA within living cells are termed "recombinant proteins". The production of a recombinant protein from its encoding DNA allows quantities of protein to be produced which are sufficient for use in laboratory studies or in large scale industrial production.

82. Recombinant protein expression requires the cloning of the corresponding DNA sequence into an expression vector containing components suitable for producing the protein in a host cell. The simplest systems are generally based on Escherichia coli ("*E. coli*"). However, mammalian proteins may not always be successfully produced by the simple prokaryotic (bacterial) machinery in *E. coli*, and therefore eukaryotic systems are also used, including yeast and mammalian cell cultures. Large polypeptides of eukaryotic origin can be toxic when expressed in bacteria, due to their aggregation and/or precipitation in the cytoplasm of the bacteria. In addition, mammalian proteins often require post-translational modifications, such as the addition of sugar groups (glycosylation) or fatty acids, and can also require help to correctly fold. Thus, recombinant protein expression is often not a simple procedure, and the expression systems have to be carefully selected and tested for a given protein before large scale production can be initiated.

The immune system and immune response - background

83. The Skilled Antibody Engineer would have had a working knowledge of the human immune system and (if necessary) could have consulted materials such as "Janeway's Immunobiology" which was widely used and highly regarded by 2007. The 6th edition of this leading textbook (Janeway & Travers, *Immunobiology, The Immune System in Health and Disease* (6th Edition) 2005) was published in 2005 ("Janeway 2005").

84. The immune system can be described has having two parts: innate and adaptive, each of which then have cellular and humoral (meaning substances found in extra-cellular fluids) components.

85. Antibodies, also known as IgGs, are produced by B cells of the adaptive immune system and bind to antigens. An antigen is any substance that can be recognised by the adaptive immune system and may be from a micro-organism or an allergen, or a component of a therapeutic such as a vaccine.

86. The binding of antibodies to their antigens triggers a number of downstream "effector functions". These effector functions include: (i) Fc-receptor mediated phagocytosis of the antigen; (ii) the activation of a cascade of enzymes, known as the complement pathways, which degrade the antigen or kill cells to which the antibody binds; and (iii) antibody dependent cellular cytotoxicity.

87. Any protein which is unfamiliar to the human immune system can generate an immune response *in vivo*.

88. Because antibodies are proteins, they themselves can generate an immune response if they are put into an alien immune system. Thus a murine (rodent) antibody injected into a human being will generate an immune response in the human. This is important when it comes to designing antibodies for use as therapeutic agents in humans.

89. Avoiding unwanted immune responses is a key part of engineering antibodies intended for use in therapy, and Skilled Antibody Engineers (this expression was used by the parties in the ASCGK and I reproduce it in this section for convenience and without modifying or qualifying my conclusions on the skilled person) involved in the development of a therapeutic antibody are conscious of the need to reduce the risk of immunogenicity. Natural human sequences in such proteins are preferable where possible, as even small changes will need to be tested to check for an unwanted immune response.

Generation of antibodies in eukaryotic systems

90. When transcribing/translating any polypeptide chain in a cell which either will be secreted from the cell or is intended to end up in various locations within the cell (for example the nucleus), the genetic code/mRNA will include nucleotides encoding a short peptide sequence at the N-terminus of the polypeptide chain that engages the cell's transport machinery to direct the polypeptide chain being translated to the right location. This short peptide sequence is commonly referred to as a 'leader sequence' or a 'signal peptide'.

91. Thus, for an antibody, the amino acid sequence that is co-translated will initially include what will be the final amino acid sequence of the antibody as well as a secretory leader sequence at the N terminus (beginning) of each heavy and light chain.

92. For a polypeptide which is to be secreted (like an antibody) the leader sequence interacts with a signal recognition particle (SRP) in the cell to guide the nascent polypeptide chain to the endoplasmic reticulum.

93. Once the polypeptide chain has been correctly deposited by the SRP, the leader sequence will be cleaved off from the rest of the polypeptide chain by a signal peptidase enzyme. The polypeptide chain will then fold into its mature configuration.

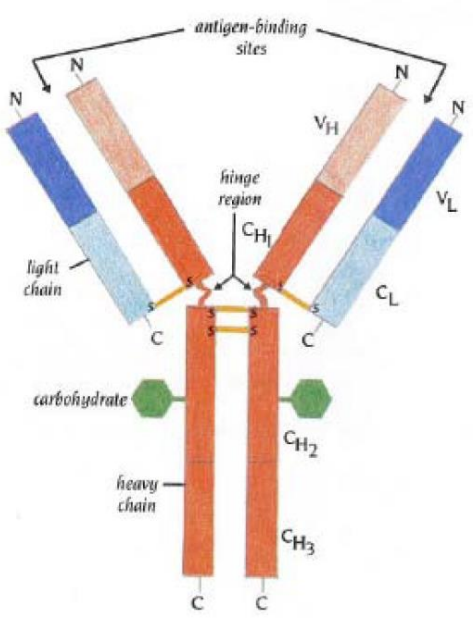
94. It is common to identify a leader sequence in some way to distinguish it from the antibody sequence, such as using italics or underlining.

95. There are many different naturally occurring leader sequences, and by 2007 there were also optimised leader sequences known. However, in some cases the leader sequence can affect expression and thereby give a better yield of a particular polypeptide.

Antibody structure and function

96. Antibodies are divided into different classes and subclasses depending on the heavy chain (described below). There are five distinct classes (also referred to as isotypes) of antibody called IgA, IgD, IgE, IgG and IgM, the heavy chains of which are known as α, δ, ε, γ and μ chains respectively. All antibody isotypes also have either a kappa or lambda light chain. The classes or isotypes differ in a number of aspects, most importantly in size and amino acid sequence. Some isotypes can consist of a combination of more than one antibody molecule (IgM and IgA), whereas others (IgG, IgE and IgD) are monomeric.

97. An IgG is made up of four chains of amino acids. There are two identical long chains, referred to as the heavy (H) chains, and two identical short chains, referred to as the light (L) chains. These are held together to create a symmetrical Y-shaped molecule which is illustrated diagrammatically below (source: Brandon and Tooze, Introduction to Protein Structure, Garland Publishing (1991)).



98. Each heavy chain (coloured red) consists of four domains or regions: three constant domains (CH1, CH2, CH3) and one variable domain (VH). The CH1 and CH2/CH3 domains are connected via a hinge domain. Each light chain (coloured blue) consists of two domains: one constant domain (CL) and one variable domain (VL). The chains are joined by disulphide (SS) bonds (coloured orange), and also associate non-covalently. The four variable domains, which are located at the N-terminal ends of the chains, form the antigen binding sites.

99. The domains are referred to as "variable" and "constant" to reflect the extent to which the amino acid sequence in them varies from antibody molecule to antibody molecule within the same animal. Thus, for example, a human being will have a large number of antibodies in their bloodstream, depending on the foreign materials (e.g. bacteria and viruses) which they have had to raise immune defences to. This will include many IgG molecules. The constant regions in one such molecule will be substantially identical to the constant regions in all the other IgG molecules his B lymphocytes produce. But the variable regions of the antibodies made to defend against, say, whooping cough will differ from the variable regions of the antibodies made to defend against, say, mumps.

100. Each antigen binding site is formed by the juxtaposition of six segments of the variable domains referred to as complementarity-determining regions (CDRs). The CDRs are also referred to as the "hypervariable regions" or "hypervariable loops" of the antibody. They differ in amino acid sequence between antibodies against different epitopes, and in addition, certain of them vary in length from one antibody to another. There are three CDRs in each of the heavy and light chain variable domains (CDRH1, CDRH2 and CDRH3 refer to the 3 CDRs in the heavy chain, and CDRL1, CDRL2 and CDRL3 refer to the 3 CDRs in the light chain). Each antibody can bind two epitopes at the same time, one on each arm. The CDRs within the variable antibody region are the major determinants of specificity and affinity. The variable regions within the Fab region are what interacts with the antigen and is responsible for binding to antigen.

101. Each arm of the Y, sometimes referred to as a fragment antigen binding (Fab) region, consists of the 4 largely conserved "framework" regions, 3 highly variable CDRs, and one constant region, for each of the heavy and light chains. The parts of the variable regions of both the heavy chains and light chains that are outside the CDRs are known as the framework regions. The framework regions of the variable domains are critical in forming the "scaffold" on which the CDRs sit, and consequently for correct display and presentation of the CDRs for binding to antigens.

102. Each IgG heavy chain has the following components:

    Framework1 – CDRH1 – Framework2 – CDRH2 – Framework3 – CDRH3 – Framework4 – CH1 – Hinge – CH2 – CH3

103. Each IgG light chain has the following components:

    Framework1 – CDRL1 – Framework2 – CDRL2 – Framework3 – CDRL3 – Framework4 – CL1

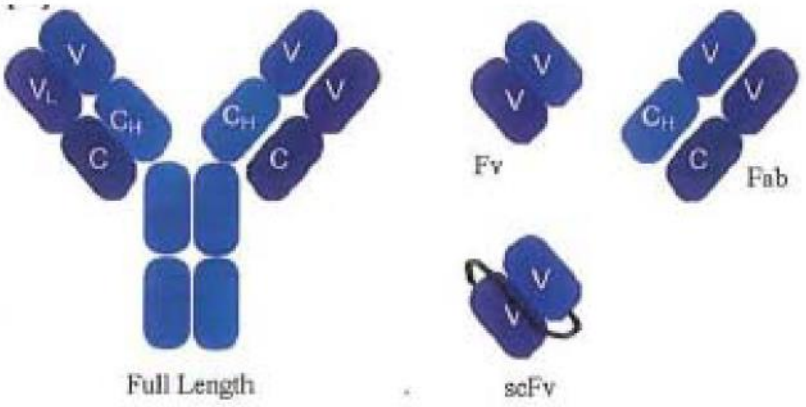
104. The Hinge region is then a chain of amino acids that differs in length between different antibody isotypes and sub-classes. The Hinge can change its orientation and allows the antibody to move and have different spatial distribution.

105. The bottom portion of the Y, consisting of the Hinge – CH2 – CH3 domains, is properly referred to as the fragment crystallisable (Fc) region. Depending on the sub-class or other features such as glycosylation, the Fc region (hinge – CH2 – CH3) can interact with Fc receptors and the complement system and determine the "effector functions" of the antibody.

106. The Skilled Antibody Engineer could have looked up the sequence of each IgG4 domain in any database or reference book. There is only one IgG4 CH1, hinge, CH2 and CH3 domain sequence. There was only one known allotype of IgG4.

Antibody fragments

107. It is possible to cut an IgG molecule into pieces or to manufacture pieces of it using recombinant methods. For example, it is possible to isolate each of the two arms. These are called "Fab" (Fragment antigen-binding) fragments. They will contain the variable domains (including the CDRs) and some of the constant domains. It is also possible to isolate the variable domains alone (i.e. the VH and VL domains): these are known as "Fv" (Fragment variable) fragments. The two variable domains in an Fv fragment can be linked together with a short chain of amino acid (called a peptide linker) to produce something which is called a "single-chain Fv" fragment or scFv (sometimes referred to as a "single-chain antibody" or SCA):



108. These types of fragment (Fab, Fv and scFv) possess some of the same properties as complete antibodies. In particular, they can bind to antigens, although they are monovalent, i.e. they only have a single binding site.

109. The term "Fd" is also sometimes used to refer to the amino acids of an antibody heavy chain including the VH1 and CH1 domains.

Antibody classes or isotypes and effector functions

110. As set out at above, antibodies are divided into different classes and subclasses depending on the heavy chain.

111. IgG and IgA are further divided into subclasses. Human IgG is divided into four subclasses which differ only slightly in their amino acid sequences: IgG1, IgG2, IgG3 and IgG4. Human IgA is divided into IgA1 and IgA2. Mouse IgG is also divided into subclasses, namely, IgG1, IgG2a, IgG2b and IgG3. Although IgG subclasses are very similar in sequence, they have different properties. Human IgG1 was the most well-known, studied, and commonly used sub-class for therapeutics at 2007 (and still is today).

112. The Fc region of an antibody mediates the effector functions of the antibody via binding to Fc receptors on the cells of the immune system. Different Fc receptors exist which show specificity for different classes and subclasses of antibody. The receptors that recognise IgG are known as Fcγ receptors (FcγRs). Before 2007, it was known that there are multiple Fcγ receptors which differ in their cell type distribution and in their affinity for IgG. One of the main differentiators between IgG subclasses in both human and mouse is the ability of the Fc regions of the different subclasses of the antibodies to bind to Fc receptors (FcRs). This in turn affects the ability of each IgG subclass to activate the various effector functions.

113. The following Figure 9.19 from page 389 of Janeway 2005 summarises and ranks the major effector functions of each isotype:

Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	–	++	++	++	++	++	–
Opsonization	+	–	+++	*	++	+	+	–
Sensitization for killing by NK cells	–	–	++	–	++	–	–	–
Sensitization of mast cells	–	–	+	–	+	–	–	+++
Activates complement system	+++	–	++	+	+++	–	+	–

Distribution	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	–	–	–	–	–	+++ (dimer)	–
Transport across placenta	–	–	+++	+	++	+/–	–	–
Diffusion into extravascular sites	+/–	–	+++	+++	+++	+++	++ (monomer)	+
Mean serum level (mg ml^{-1})	1.5	0.04	9	3	1	0.5	2.1	3×10^{-5}

Fig. 9.19 Each human immunoglobulin isotype has specialized functions and a unique distribution. The major effector functions of each isotype (+++) are shaded in dark red, whereas lesser functions (++) are shown in dark pink, and very minor functions (+) in pale pink. The distributions are marked similarly, with actual average levels in serum being shown in the bottom row. *IgG2 can act as an opsonin in the presence of an Fc receptor of the appropriate allotype, found in about 50% of white people.

114. One effector function is the ADCC (Antibody Dependent Cellular Cytotoxicity) effector function. ADCC is a process of cell killing via triggering apoptosis (programmed cell death) of pathogens or virus-infected host cells, and is mediated by an immune cell binding, via the Fc receptors on its surface, to the Fc region of IgG molecules bound to surface antigen.

115. There are differences in binding affinity of the IgG class antibodies between the different types of Fcγ receptors. For example, IgG2 antibodies do not bind most Fcγ receptors at all, but bind some weakly. Additionally, it was known that IgG4 does not activate complement at all, IgG2 does activate complement to some extent but less than IgG1 and IgG3. Also, IgG4 binds Fcγ receptors with a low affinity, although greater affinity than IgG2 (and a much lower affinity than IgG1 and IgG3).

Polyclonal and monoclonal antibodies

116. It has long been known that it is possible to obtain enriched preparations of antibodies for research purposes by inoculating a laboratory animal with an antigen of interest and purifying IgG from its serum once the animal has had the opportunity to produce an antibody response. Even though stimulated by a single antigen, these types of antibodies are “polyclonal” because they comprise mixtures of different antibodies, each of which may bind to different epitopes on the same foreign antigen due to differences in their variable regions.

The complement pathways

117. The complement system is part of the humoral component of the innate immune system of humans. It is one of the first lines of defence of the immune system, helping to clear microbes and damaged cells from the body and remove invading pathogens, and plays an essential role in maintaining and regulating inflammatory responses in the body. By 2007, complement was known to contribute to or mediate the pathology of various diseases, either via excessive/ undesirable activation of the system (for instance by autoantibodies) or via abnormalities in the regulation of the system.

118. There are three pathways for complement activation: the Classical, Alternative and Lectin pathways. The Classical pathway is activated via C1q binding to antibodies bound to the surface of pathogens. The Lectin (Mannose-Binding Lectin, or MBL) pathway is activated by direct MBL binding to the surface of pathogens without requiring opsonisation by antibodies. The Alternative pathway involves spontaneous activation of complement component C3, which can lead to direct opsonisation of pathogens by C3 deposition. All three pathways of activation require C3 activation in order to trigger the downstream pathways following C3 activation. The three pathways are summarised in Fig. 1 below (source: Janeway 2005):

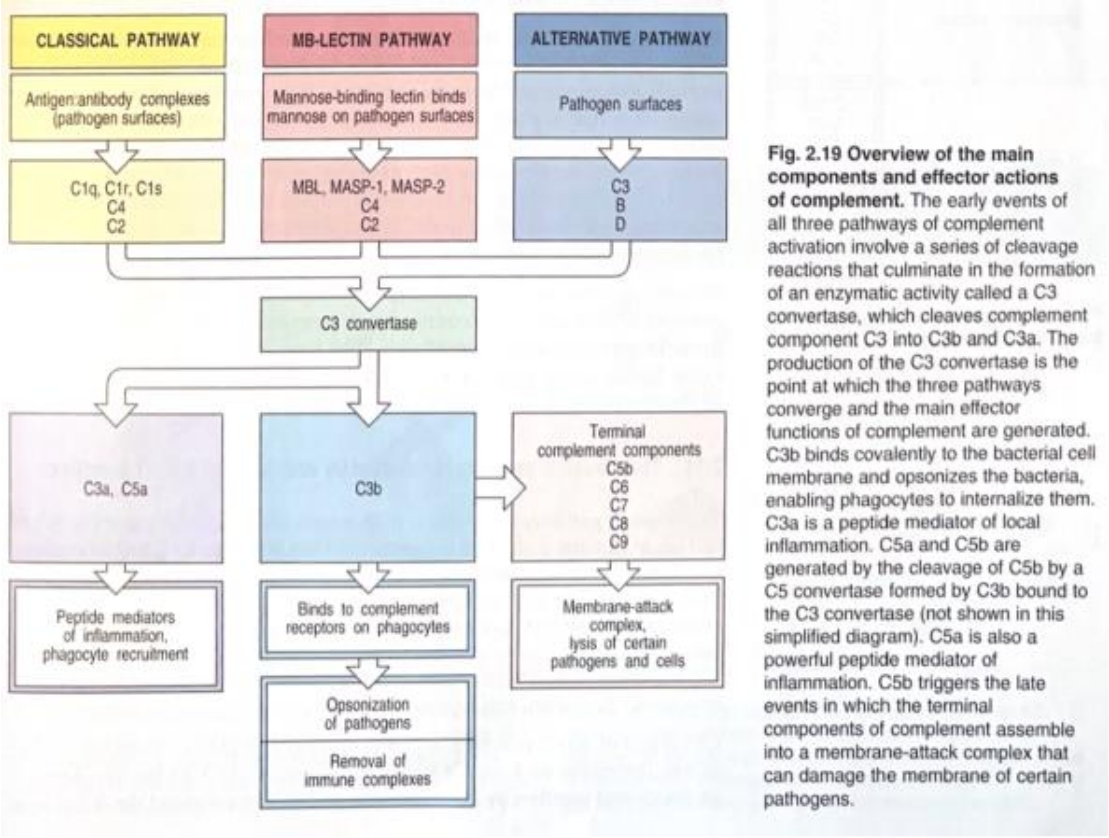


Fig. 2.19 Overview of the main components and effector actions of complement. The early events of all three pathways of complement activation involve a series of cleavage reactions that culminate in the formation of an enzymatic activity called a C3 convertase, which cleaves complement component C3 into C3b and C3a. The production of the C3 convertase is the point at which the three pathways converge and the main effector functions of complement are generated. C3b binds covalently to the bacterial cell membrane and opsonizes the bacteria, enabling phagocytes to internalize them. C3a is a peptide mediator of local inflammation. C5a and C5b are generated by the cleavage of C5b by a C5 convertase formed by C3b bound to the C3 convertase (not shown in this simplified diagram). C5a is also a powerful peptide mediator of inflammation. C5b triggers the late events in which the terminal components of complement assemble into a membrane-attack complex that can damage the membrane of certain pathogens.

119. In simple terms, the components of the classical pathway are labelled "C1" to "C9", although these names were attributed in order of discovery rather than in order of mechanism. The complement components downstream of C5 (C6-C9) become deposited on the surface of cells and generate the membrane attack

complex (MAC), which generates pores in the cell membrane leading to the destruction of target cells.

120. A functioning immune system is important to allow the body to fight infection. However, problems can arise where the immune system does not function properly, including where the complement system is activated excessively or is not properly regulated. This can be called "complement-mediated disease".

Complement activation

121. It has been known since the late 1980s/early 1990s that IgG class antibodies have different abilities to bind C1q and activate the complement pathway. As noted above, it was known that IgG4 does not activate complement at all, and IgG2 does activate complement to some extent but less than IgG1 and IgG3.

122. For both Fcγ receptor binding and complement activation the desirability of these effects will depend on the intended function of the antibody i.e. whether the goal is to kill a target cell or to block an unwanted binding interaction. For antibodies intended to stimulate an immune response against the target cells, for example antibodies against cancer cells, Fcγ receptor binding and complement activation may be advantageous. However, for blocking antibodies intended as a chronic treatment of conditions associated with an overactive immune system, one would normally want to avoid these effects where possible. The target and purpose of the antibody will therefore affect the choices made by the antibody engineer.

Antibody engineering

123. By 2007, the Skilled Antibody Engineer would have had access to and understood the basics of molecular biology. The Skilled Antibody Engineer would also have understood the basics of biochemistry, such as how enzymes work and how proteins fold. The standard molecular biology textbook available to the Skilled Antibody Engineer by that time included Molecular Biology of the Cell by Alberts et al. If required, they may have consulted biochemistry textbooks, such as Biochemistry by Stryer et al., for further information on that topic. Although the Skilled Antibody Engineer may have had reference to such sources for a specific question, all of the information in such a biochemistry textbook (beyond what is covered in a basic undergraduate science degree) would not necessarily been commonly known across the field.

124. In 2007, the majority of antibody engineering expertise required hands-on experience. In many companies and research centres the basic principles of antibody engineering would have been set out in internal know-how guides or lab manuals. Many of the basic principles of antibody engineering were developed in the 1990s and had not materially changed since then. Example resources that would have been available at March 2007 include texts such as the following:

    (a) "Molecular Cloning: A Laboratory Manual" ("Maniatis") by J. Sambrook and D. Russell, Third Edition 2001.

    (b) "Phage Display: A Laboratory Manual" by Barbas et al, First Edition 2001.

(c) "Using Antibodies: A Laboratory Manual" by Harlow et al, First Edition, 1998.

(d) "Antibody Engineering" by R. Kontermann and S. Dübel, First Edition 2001.

(e) "Antibody Engineering" by C. Borrebaeck, 1995.

(f) "Antibody Engineering A Practical Approach" by J. McCafferty, H. Hoogenboom and Chiswell, 1996 ("Antibody Engineering by McCafferty").

125. There were a number of databases freely available containing sequence information for proteins, including antibodies, and which could be used to identify sequences where relevant. These databases would include the following non-exhaustive list for use in an antibody project:

(a) ImMunoGeneTics information system, IMGT which is run by the French Institute of Human Genetics.

(b) Universal Protein Resource (UniProt) which is run by a consortium including the European Bioinformatics Institute.

(c) GenBank, operated by the U.S. National Center for Biotechnology Information (NCBI) run by the U.S. government's National Institutes of Health.

126. The Skilled Antibody Engineer had access to and would have routinely used bioinformatics tools or databases, including for aligning antibody sequences (that is, lining up two or more amino acid (or nucleic acid) sequences to identify where they are the same and where they differ). A range of bioinformatics tools were available by 2007. These included ExPASy (and the affiliated Swiss-Prot database accessible through ExPASy) and the National Center for Biotechnology Information (NCBI). These were open-source software packages that provided information and tools for amino acid sequence alignments and references to crystal structures where available. BLAST (Basic Logical Alignment Search Tool) was another commonly known tool.

127. While these databases and tools are helpful, it is widely known that there are errors in databases as most information is self-submitted and not independently verified.

Overview

128. In an antibody development project, once a target antigen has been identified (and ideally understood), the process for antibody engineering involves:

(a) constructing and/or selecting a monoclonal antibody with the desired specificity and affinity for the target, most likely using hybridomas from immunised mice or phage display techniques;

(b) optimising the antibody, including possibly to further enhance binding (via phage display), to adjust its effector functions, for stability, production and yield;

(c) generating a transiently and/or stably transfected cell line that produces the antibody recombinantly, generally using HEK or CHO cell lines, and then purifying the antibody and confirming its affinity and specificity; and

(d) conducting preclinical testing *in vitro* and in animal models, including to assess the antibody's efficacy and safety.

129. Assuming the antibody was derived from a murine or non-human other animal antibody-producing B cell, it will be necessary to "humanise" the antibody as part of the process above.

130. In a project to recreate a known antibody, not all of the above steps would be required.

Hybridoma

131. The most common approach for obtaining an antigen-specific antibody in 2007 was (and remains today) by hybridoma. A hybridoma is an antibody-producing cell line derived from natural B cells. Unless working with a disease involving human plasma (blood) cells, it is difficult to access human antibody-producing B cells directly, and so host animals (most commonly mice or rats) were and are used instead.

132. In the hybridoma process, the host animal is first immunised to stimulate an immune response and the production of antibodies against the antigen. This is (and was in 2007) usually done by injecting a recombinant protein or a cell over-expressing the target into the animal, and then using an adjuvant to boost the immune response and provide a higher concentration of antibodies. Once antibody production has been confirmed, antibody-producing B cells are harvested from the animal (usually from the spleen) and fused with (usually myeloma – immortal cancerous B cell line) cells to form hybrid cells, called hybridoma cell lines. These hybridoma cells are then cultured in a selective medium that allows only the fused hybridoma cells to survive. The supernatant (liquid portion of the cell culture that remains after the hybridoma cells have been removed by centrifugation and filtration, and contains the antibodies secreted by the cells) is then collected and screened to identify the antibody that recognises the antigen/epitope. Once a suitable hybridoma clone has been identified, the antibody can then be cloned and can be produced as a recombinant antibody.

Recombinant antibodies

133. Once a preferred antibody or antibody-fragment has been identified via hybridoma (or other available techniques), and the genes encoding the antibody or antibody fragment have been cloned, they can be inserted into an appropriate expression vector, which is introduced into a suitable host cell for production, and expressed recombinantly (as discussed at above).

Making antibodies for human use

134. Köhler and Milstein's technique only works efficiently with murine hybridoma cells. Human cell-derived hybridomas are not as productive as the mouse equivalents and are unstable (meaning they will stop producing antibody after a period of time). In addition, it is difficult to select human antibodies against predefined antigens since it is not possible to immunise human volunteers with human-derived molecules in most cases.

135. Therapeutic antibodies that may need to be given more than once are therefore generally modified to more closely resemble naturally-occurring human antibodies, while still retaining the sought after antigen-binding properties. This is because, although murine (and other non-human animal) antibodies can and have been used in the treatment of humans, these can often be given to patients only once or twice before the body recognises the proteins as "foreign" and rejects them, for instance by the production of anti-drug antibodies. An immune response to proteins that are foreign (i.e. not natural to the human body) is known as immunogenicity. By 2007, a number of methods had been devised of obtaining murine monoclonal antibodies and then making them more compatible with the human immune system. The challenge was to do this without loss of specificity and affinity.

Antibody humanisation

136. To obtain an intact therapeutic antibody for use in humans, "humanisation" of antibody produced from hybridoma (or the addition of an Fc domain to antibody fragments from phage display), is required as part of or after recombinant production.

137. One approach to making a non-human antibody more human was to fuse the antigen-binding variable region from a mouse antibody to a human constant region to create a "chimeric antibody". Chimeric antibodies are monoclonal antibodies in which the V_H and V_L regions from the original antibody (e.g. mouse or rat) are joined using recombinant DNA technology to a constant region of an antibody from another species (usually human). Since the constant region typically has limited or no effect on antigen binding, the specificity of the original monoclonal antibody will be retained. The addition of a human constant region reduces, but does not entirely eliminate the anti-drug antibody (such as HAMA) responses.

138. Another approach, although more complex, was called "CDR grafting". CDR grafted antibodies are antibodies in which a greater proportion of the amino acid sequence of the antibody is derived from human. CDR grafting involves identifying the amino acids in the CDRs of the antibody raised (often the murine form) and inserting them into the place of the corresponding CDRs of a human antibody framework. The resulting antibody should bind the desired target (because it has the antigen binding specificity of the murine antibody) but reduce the risk of triggering the body's immune system as a result of foreign amino acid sequences because the framework is human.

139. The creation of CDR-grafted humanised antibodies often requires a number of further steps, including individual changes to amino acids in the human framework sequence to ensure proper antibody folding and antigen recognition.

140. In the early 1990s humanisation was still a fairly new field and a number of papers were published demonstrating the humanisation of novel antibodies. By the mid-1990s the basic principles of humanisation were in place, and several humanised monoclonal antibodies were on the market by the late 1990s. By the early 2000s it was less common to publish on a typical humanisation process unless an interesting feature had been identified in the process.

Steps in preparing antibodies for human use

141. Preparing a chimeric antibody, with the entire variable region of the murine antibody grafted on to a human constant region can provide the antibody engineer with quick and useful information such as whether the chimeric antibody retained the binding affinity of the original murine antibody or whether the chimerisation process reduced or destroyed the binding affinity. If the chimeric antibody displayed appropriate binding affinity then it could be used as a control as the humanisation process continued.

142. During a typical CDR grafting process the first step is for the variable region sequence and CDRs of the non-human (usually murine) antibody to be identified. The antibody engineer working on a project would typically choose a single scheme to identify the CDRs, with Kabat being by far the most common. The Kabat sequence variability definition was the most widely used CDR definition in 2007 (including as compared to the "structural variability" definition of Chothia and Lesk).

143. The CDRs taken from the non-human antibody are then used to replace the CDRs of a human variable region framework to make a humanised antibody. To implement this the Skilled Antibody Engineer must select a suitable 'human framework donor'. The very earliest humanisations would compare the murine variable domain to existing databases of human variable region sequences, and select existing antibody variable regions (VH and VL) as frameworks on the basis of sequence homology, which would therefore be expected to retain the greatest binding affinity. By 2007 there was a greater awareness that structural information might be more important than the precise homology of the amino acids, and the antibody engineer might have also considered the structure and configuration of the available frameworks. For each domain/region of the antibody there is a number of naturally occurring human frameworks, referred to as human 'germlines' and over time it became more common to focus on human germlines rather than other existing antibodies. The advantage of using a naturally occurring human framework is that it reduces the risk of immunogenicity. The sequences of the human germlines can be taken from the databases discussed above.

144. The Skilled Antibody Engineer comparing sequences would have understood that, in the process of CDR grafting, it is sometimes necessary to make changes to the framework region (and, in extreme cases, to make changes within a CDR), for instance if an antibody is not folding well after grafting a CDR into a

framework. The Skilled Antibody Engineer would not apply any theory of CDR-lengths too rigidly.

145. In addition to the CDRs being grafted into the human framework, the antibody engineer may consider whether any 'framework back mutations' were necessary. While the sequence of the CDRs is critical for binding a target, the structure of the framework regions can impact the conformation of the CDRs and thereby also affect the binding affinity. When inserting non-human CDRs into a human framework the differences in the human framework (as compared to the non-human framework) can result in the CDRs not being held in the right conformation to bind the target. In these cases, the antibody engineer would identify amino acids that differ between the human and non-human frameworks at locations that were known to be potentially critical for the conformation of the CDRs, and then systematically change these back to the non-human sequence and test the impact on binding affinity.

146. Humanisation is an empirical field, and the only way to know the impact of any antibody modifications (including any humanisation step) is to test the antibody. Antibody engineers would want to test the binding affinity of the humanised antibody and any variants they are considering.

147. If a CDR-grafted antibody without any framework back mutations has retained binding affinity similar to the original non-human antibody then there is generally no need to consider further changes to the antibody in relation to binding. If an antibody with CDR grafts has a lower affinity than the original non-human antibody, but framework back mutations, for instance, significantly improve the binding affinity, then such mutations may be retained. On the other hand, if framework back mutations do not appreciably improve binding affinity they are unlikely to be retained, as the preference would be to reduce the non-human content and thereby minimise the immunogenicity risk.

148. Throughout an antibody engineering project, the Skilled Antibody Engineer would be guided by their experience and preferences, including in their selection of an appropriate vector and host cell, secretory leader sequence, preferred framework sequence, and additional modifications they would be prepared to make, based on their experience in previous projects.

Fc domain engineering

149. In addition to the basic principles of antibody engineering and humanisation outlined above, it is possible to develop modifications of the antibody elsewhere which could improve the properties of antibodies for a particular purpose, for example Fc domain engineering to alter the effector function.

150. These developments included work on engineering the Fc region to alter the Fc effector function activation and properties of humanised antibodies. To reduce the effector functions of a candidate antibody during a humanisation and/or optimisation process, the antibody engineer could have considered various options, including:

(a) Using an Fc domain that lacks sugar domains or has naturally low Fcγ receptor binding (IgG2) or complement activation (IgG4) depending on which effector function the project was more concerned with.

(b) Using a fragment of the antibody instead of a full length antibody (i.e. removing the Fc domain entirely), though this would impact significantly the half-life of the molecule.

(c) Using an IgG1 Fc region but introducing point mutations in the Fc region such as the LALA mutation, where two leucine (L) residues are replaced with alanine (A). This mutation is denoted L234A/L235A[19] and so abbreviated to LALA. It was known that this mutation reduced Fcγ receptor binding and complement activation in IgG1 antibodies. While IgG1 antibodies with these mutations did retain both Fcγ receptor binding and complement activation they are significantly reduced compared to the native form of IgG1. These mutations were well known by the late 1990s.

Pre-clinical validation

151. Post-humanisation pre-clinical validation involves studying the antibody.

152. Pre-clinical validation can involve evaluating the antibody and performing stability studies under relevant conditions (including at different pHs, temperatures or concentrations), assessing any risk of aggregation, degradation, or other factors affecting shelf life, and generally seeing how the antibody is behaving, as well as considering whether the sequence could impact expression yields during manufacturing. That is: properties that may be investigated include manufacturability or stability of the antibody, as well as the efficacy or immunogenicity of the antibody *in vivo*.

153. Depending on the project and its context this preclinical validation could be a relatively straightforward process or could be a more complex and time consuming exercise. In 2007 this was a process that a Skilled Antibody Engineer would have been familiar with. They may have engaged an analytics group to assist.

154. Further aspects of pre-clinical validation are covered in the disputed CGK points, below.

Antibody controls in experimentation

155. One would at least generally want to use as a negative control an antibody with the same constant region as the test antibody but a different variable region such that the only difference will be that the control antibody will have different antigen binding properties than the test antibody.

Antibody clone names

156. To identify the best candidate antibod(y/ies) to take forwards in the development process, a number of hybridomas are generated and then plated onto an ELISA

plate, ideally with just a single hybridoma in each well. The hybridomas are cultured for a time, and then the antibodies secreted by the individual hybridomas will be screened to select the antibody with the best affinity and specificity for the desired target.

157. For early research and development, the antibody is commonly assigned a name based on the well of the ELISA plate in which the hybridoma was cultured. So if the preferred antibody was produced by the hybridoma in plate number 1, row A, column 1, then the antibody will be given a name like "1A1" or "1A-1". This is known as a "clone name".

158. If a clone name is used to refer to an antibody, where it is helpful to distinguish between the murine, chimeric and humanised variants, terms such as m1A1, ch1A1 and h1A1 can be used, or 1A1 scFv when discussing a single chain Fv.

159. At a later stage in the antibody's development the company developing it would apply for an antibody having a particular amino acid sequence to be given a formal International Non-proprietary Name (INN) by the World Health Organization. An INN should refer to a single amino acid sequence. Once an INN was granted it would more commonly be referred to by the INN.

160. Further nuances of this topic were the subject of one of the disputed CGK points: see below.

Disputed CGK

161. The parties identified three disputed areas of CGK (they broke these into sub-points in some instances but doing so is not necessary to my analysis):

    i) Clone names;

    ii) "Pre-clinical validation" of antibodies and "sequence liabilities";

    iii) Knowledge of eculizumab.

Clone names

162. This issue matters because it is one of the factors going to the skilled person's understanding of references to "5G1.1" in the prior art.

163. It was common ground (see above) that although it was not a universal practice, clone names like 5G1.1 often originated from the original well on an ELISA plate where an antibody was first found, at which stage it would be a murine hybridoma. The letters and numerals would denote the plate, the row and the well. The dispute was about how such a name would be used later and what it might be used to describe.

164. Alexion's position was that such clone names would as a matter of CGK be understood to refer to the original murine clone. It said, based on Prof Nimmerjahn's evidence, that using them for e.g. a humanised antibody or other derivative of the original clone would be confusing, though it accepted that there were instances of that sort of use.

165. The Defendants' position, based on the evidence of Mr Buss, was that clone names followed antibodies through their development so that e.g. 5G1.1, even when used without qualification, could refer to the humanised antibody if that was the stage of development that had been reached.

166. The evidence covered a large number of uses relevant to this point, some concerning eculizumab and others not. In addition to the use of the original plate/well designation, there were numerous instances where an expression such as h5G1.1 would be used, with the "h" denoting humanised (see again the agreed CGK, above). Sometimes the original clone name was used without this disambiguation but in circumstances when it plainly did mean specifically a humanised antibody.

167. Neither side suggested that the practice of using clone names was standardised or consistent. It clearly was neither. That being so I do not think there can be any relevant CGK as to what a clone name *necessarily* meant. Rather, the CGK was that clone names tended to arise from the original hybridoma's well as described above, and then were used in a variety of ways, it being necessary to rely on the context to decide what was being communicated in any given situation. Sometimes it would mean the original murine version, sometimes a humanised version, sometimes as a more general designator of the family of versions created during the development process. I do not think there were any relevant instances shown to me where there was a complete lack of surrounding context to inform an understanding of what was said, even if such context as there was did not entirely dispel any ambiguity.

Pre-clinical validation/sequence liabilities

168. This aspect of CGK goes to the obviousness case over Tacken, where the Defendants' case included it being obvious to change the amino acid at position 38 of the light chain (a framework residue) from arginine to glutamine, i.e. from murine to human.

169. Alexion in its closing written submissions dealt with the issue in the context of Tacken whereas the Defendants addressed it in the context of CGK. I do not think it makes any difference where the relevant text appears in the parties' skeletons, but I must bear in mind that what I am considering is what was CGK. Plugging my conclusions into the analysis of Tacken is conceptually and practically a different thing.

170. The disputes under this heading were covered by a number of the descriptions in the list of disputed CGK, in a way which I found a little unhelpful and almost cryptic in some cases. In fact the material disputes are quite narrow, I think.

171. Thus, it was CGK to the antibody engineer that problems could arise with the development of therapeutic antibodies. There were a variety of problems that could arise, including but not limited to unusual amino acid sequences in the framework regions (the point relevant to this judgment), deamidation sites, oxidation sites and glycosylation sites.

172. I was satisfied that "Antibody Engineering" by McCafferty and others (1996) reflects the CGK on the nature of the problem relevant to me (Mr Buss identified it as a CGK source in his first report and I accept that evidence and anyway it is referred to in the ASCGK as such a source, although I accept that does not automatically make every part of its contents such). Prof Nimmerjahn was cross-examined on pages 158 to 160 and did not disagree with their contents as CGK. I am accordingly satisfied that it was part of the CGK that amino acid differences between murine and human sequences should be examined and where there was an unusual amino acid sequence in the framework regions of mouse or human it should be studied. The way in which a decision as to which to use should be reasoned (though ultimately it was an empirical matter that needed testing) is also set out in McCafferty and it was CGK that it involved considering the achievement of good binding while retaining, as much as possible, human framework regions matching the sequence from natural human antibodies. It should be noted that McCafferty calls out position 38 as being significant, in Table 6.

173. However, McCafferty does not deal with what was the key disputed point, which is whether the skilled person would as a matter of CGK address a risk identified early and prophylactically in pre-clinical work (which in the present case would mean by trying out the antibody with the human residue at position 38 – see below), or wait to see if there was a problem later on.

174. On that point, I prefer the evidence of Mr Buss because it was founded on much more real world experience of actually developing antibodies towards clinical use. It also makes logical good sense. Scrutinising the sequence for this sort of issue is an analytical exercise and plainly would be done at an early stage to assess risk. In relation to unusual framework residues it would not make sense to hope for the best in the knowledge that a problem might emerge downstream when the commitment to a particular sequence was greater, rather than doing a simple test early on.

175. I am conscious that I am making a finding that something was CGK (derisking in relation to unusual framework residues early) when the textbook relied on does not address the point as such. But I think that is just because this is CGK of a very practical on-the-job kind and not the sort of thing that appears in textbooks. At the very least, which would be good enough for this part of the Defendants' obviousness case, it must have been CGK that early de-risking was a sensible option.

176. A subsidiary issue on this topic was whether certain online resources made available by Prof Andrew Martin and related to an analysis tool called abYsis were CGK. This was in fact not part of the Defendants' case, as it turned out. They relied on McCafferty and I have held that that was good enough both in general in terms of early derisking and specifically to flag position 38 as a potential sequence liability. In case I have misunderstood the position, I would have found that Prof Martin's resources were not CGK, since, for example Prof Nimmerjahn had not heard of them. Some further confusion arises because I am not clear whether *any* version of abYsis or Prof Martin's materials even existed at the priority date, or whether there was a version then but Mr Buss used a later version (he certainly used a post-priority version for a very limited and ultimately

irrelevant purpose, as I touch on below). It is unimportant: it was not CGK at the priority date.

Knowledge of eculizumab

177. Eculizumab was clearly CGK to the skilled team as I have found it to be; Alexion did not dispute that.

178. As I have already explained when dealing with the skilled team, I also consider that eculizumab would be CGK to the skilled person as defined by Alexion, for reasons that I have mentioned when dealing with the identity of the skilled person or team above: Alexion conceded that its skilled person (an antibody engineer interested in complement-mediated disease) would know about the need for treatments for PNH and that being so I conclude, though Alexion would not concede, that eculizumab would also inevitably be CGK.

THE PATENT SPECIFICATION

179. The Patent is entitled "Treatment of paroxysmal nocturnal haemoglobinuria patients by an inhibitor of complement".

180. No claim to priority is made in these proceedings for any date earlier than the filing date of 15 March 2007.

181. In the "Background" section, [0003] states:

> [0003] Eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5:[11] In a preliminary, 12-week, open-label clinical study in 11 PNH patients, eculizumab was shown to reduce intravascular hemolysis and transfusion requirements.[12] However, this unblinded study involved a small number of patients with no control arm and without protocol-driven transfusion standards.

182. In the "Summary" section, [0005] through [0009] state:

> [0005] It has been surprisingly discovered that certain aspects of quality of life were unexpectedly improved by the treatment of PNH patients with eculizumab. Furthermore, these improvements in the quality of life were independent of transfusion. The improved aspects include, e.g., global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss and insomnia. Improvement was also seen in nausea and vomiting, diarrhea, constipation, and financial difficulties but did not reach the level of statistical significance. Because the treated patients remained anemic throughout their treatment, it was unexpected that all of these improvements would have been seen because they were previously thought to be a result of the patient being anemic. Although not wishing to be bound by any theory, it appears that some of the symptoms are likely due, at least in part, to hemolysis and release of hemoglobin into the bloodstream and do not result solely from the patient being anemic. The

> treatment with eculizumab decreases the amount of lysis thereby limiting hemoglobin release into the bloodstream, thereby apparently resulting in the improvements seen in the treated patients' quality of life. The results presented herein indicate that any treatment that decreases hemolysis in a patient will result in an improvement in the quality of life of said patient.
>
> [0006] In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits complement or inhibits formation of C5b-9.
>
> [0007] In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.
>
> [0008] In certain aspects, the application provides a method to improve at least one aspect of the quality of life of an anemic patient whose anemia results at least in part from hemolysis, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis, wherein said patient remains anemic. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.
>
> [0009] In certain aspects, the application provides a method of prolonging the health-adjusted life expectancy of a patient comprising administering to said patient in need thereof a compound which inhibits formation of C5b-9. In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman. In certain embodiments, said patient suffers from paroxysmal nocturnal hemoglobinuria.

183. [0010] states:

> [0010] In certain aspects, the application provides a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

184. [0019] through [0020] state:

> [0019] In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises an altered constant region, wherein said antibody or antigen-binding fragment exhibits decreased effector function relative to an anti-CDCP1 antibody with a native constant region. In certain embodiments, decreased effector function comprises one or more properties of the following group: a) decreased antibody-dependent cell-mediated cytotoxicity (ADCC), and b) decreased complement dependent cytotoxicity (CDC), compared to an anti-CDCP1 antibody with a native constant region. In certain embodiments, the altered constant region comprises a G2/G4 construct in place of the G1 domain.
>
> [0020] In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, and wherein the light chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region consists of SEQ ID NO: 1 and the light chain variable region consists of SEQ ID NO: 3. In certain embodiments, the pharmaceutical composition comprises eculizumab. In certain embodiments, the pharmaceutical composition comprises pexelizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain consists of SEQ ID NO: 2 and the light chain consists of SEQ ID NO: 4.

185. The Defendants rely on [0020] in particular because, they say, it identifies eculizumab, pexelizumab and an antibody according to the claims, separately and distinctly.

186. In the "Detailed Description" section, [0044], contained in the sub-heading "*III The Complement System*", states:

> [0044] The beneficial effect of anti-C5 mAb has previously been reported in several experimental models including myocardial reperfusion (Vakeva et al., 1998), systemic lupus erythematosus (Wang et al., 1996) and rheumatoid arthritis (Wang et al:; 1995); as well as in human clinical trials (Kirschfink, 2001) of autoimmune disease, cardiopulmonary bypass and acute myocardial infarction.

187. In the sub-heading, "*V Inhibitors of the Complement Cascade*", [0054], [0057], [0064] and [0074] state:

> [0054] In certain embodiments, any compound which binds to or otherwise blocks the generation and/or activity of one or more complement components can be used in the present methods. In certain embodiments, a complement inhibitor may be a small molecule (up to 6,000 Da in

> molecular weight), a nucleic acid or nucleic acid analog, a peptidomimetic, or a macromolecule that is not a nucleic acid, a serine protease inhibitor, or a protein. These agents include, but are not limited to, small organic molecules, RNA aptamers including ARC187 (which is commercially available from Archemix Corp., Cambridge, Mass.), L-RNA aptamers, Spiegelmers, antisense compounds, molecules which may be utilized in RNA interference (RNAi) such as double stranded RNA including small interfering RNA (siRNA), locked nucleic acid (LNA) inhibitors, peptide nucleic acid (PNA) inhibitors.
>
> …..
>
> [0057] Suitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., U.S. Patent 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Patent 5,660,825). U.S. Patent 6,355,245 teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components.
>
> …..
>
> [0064] A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage. This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies which are specific to human complement are known (U.S. Patent 6,355,245). These antibodies disclosed in U.S. Patent 6,355,245 include a preferred whole antibody (now named eculizumab). A similar antibody against mouse C5 is called BB5.1 (Frei et al., Mol. Cell. Probes. 1:141-149 (1987)). Antibodies to inhibit complement activity need not be monoclonal antibodies. They can be, e.g., polyclonal antibodies. They may additionally be antibody fragments. An antibody fragment includes, but is not limited to, an Fab, F(ab'), F(ab')2, single-chain antibody, and Fv. Furthermore, it is. well known by those of skill in the art that antibodies can be humanized (Jones et al., Nature 321:522-5 (1986)), chimerized, or deimmunized. The antibodies to be used in the present disclosure may be any of these. It is preferable to use humanized antibodies.

U.S. Patent 6,355,245 is Evans, so this is where the Patent says that eculizumab is disclosed as a whole antibody in Evans (incorrectly, as it turns out).

> …..
>
> [0074] This disclosure also provides monoclonal anti-C5 antibodies. A monoclonal antibody can be obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations

> that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are often synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. Monoclonal antibodies may also be produced in transfected cells, such as CHO cells and NS0 cells. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and does not require production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler et al., Nature 256:495-497 (1975), or may be made by recombinant DNA methods (see, e.g., U.S. Patent Nos. 4,816,567 and 6,331,415). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature 352:624-628 (1991) and Marks et al., J. Mol. Biol. 222:581-597 (1991), for example.

188. There is a long section, the details of which were not explored in any detail at trial, from [0100] under the heading of "EXEMPLIFICATION", which is all about the TRIUMPH work.

189. There was mention in argument of [0104], which states:

> [0104] Patients were randomly assigned on a one-on-one basis to receive either placebo or eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.) within 10 days of the qualifying transfusion. Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7± 1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

190. Under the "Discussion" heading, [0125] and [0132] state:

> [0125] Chronic intravascular hemolysis with periods of acute exacerbation are the classical manifestations of PNH, frequently resulting in anemia, the need for transfusions to sustain hemoglobin levels, and deterioration in quality of life. In the phase III pivotal TRIUMPH study, we examined the effect of terminal complement inhibition with eculizumab on hemoglobin levels and transfusion requirements in patients with PNH. Forty-nine percent of patients treated with eculizumab over the 6-month period demonstrated stabilization of hemoglobin in the absence of transfusions compared to no patients in the placebo arm of the trial. Over 50% of eculizumab-treated patients were transfusion independent during the entire study compared to none in the placebo arm, and the overall mean

> transfusion rate was reduced by 73%. Moreover, even in patients who did not achieve transfusion independence, eculizumab treatment was associated with a 44% reduction in the rate of transfusion (data now shown).
>
> …..
>
> [0132] The present invention provides among other things treatment with an inhibitor of complement. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

191. [0133] under the "Discussion" heading provides the list of all publications and patents mentioned, including:

> [0133] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.
>
> …
>
> 10. Rosse WF. Paroxysmal nocturnal hemoglobinuria. Hoffinan. New York: Churchill Livingstone, 2000: 331-342.
>
> …
>
> 12. Hillmen P, Hall C, Marsh JC et al. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 2004;350:552-9.

192. In the "Sequences" section, [0134] lists the sequences as follows:

> SEQ ID NO: 1 -Eculizumab VH
>
> QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPG
> SGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYF
> DVWGQGTLVTVSSA

SEQ ID NO: 2 - Eculizumab Heavy chain

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPG
SGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYF
DVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE
RKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP
SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK

SEQ ID NO: 3 - Eculizumab V_L

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRT

SEQ ID NO: 4 - Eculizumab Light chain

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

193. [0135] in the "Sequences" section states that the "invention furthermore comprises the following items" and includes:

> 89. The method of item 88 wherein said antibody is eculizumab.

194. Item 89 is dependent on 88, 87 and 68. 68 is a method of treatment claim in keeping with the TRIUMPH work. So there is no "item" relating to eculizumab as a product *per se*.

Claims in issue

195. The claims in issue are claims 1 and 2.

196. Claim 1 is:

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

197. Claim 2 is:

> A pharmaceutical composition comprising the antibody of claim 1.

CLAIM CONSTRUCTION

198. As I have already mentioned, equivalence is not relied on so I am just dealing with purposive claim interpretation, which is said by the Defendants to be assisted by reference to the file history.

Basic law

199. There was no dispute that the basic approach is identified by the Court of Appeal in *Saab Seaeye v. Atlas Elektronik* [2017] EWCA Civ 2175 at [18]-[19]:

> 18. There was no dispute about the principles which apply to the construction of patent claims. Both parties relied, as did the judge, on the summary in this court's judgment in *Virgin Atlantic v Premium Aircraft* [2010] RPC 8 at [5]:
>
> (i) The first overarching principle is that contained in Article 69 of the European Patent Convention.
>
> (ii) Article 69 says that the extent of protection is determined by the claims. It goes on to say that the description and drawings shall be used to interpret the claims. In short the claims are to be construed in context.
>
> (iii) It follows that the claims are to be construed purposively – the inventor's purpose being ascertained from the description and drawings.
>
> (iv) It further follows that the claims must not be construed as if they stood alone – the drawings and description only being used to resolve any ambiguity. Purpose is vital to the construction of claims.
>
> (v) When ascertaining the inventor's purpose, it must be remembered that he may have several purposes depending on the level of generality of his invention. Typically, for instance, an inventor may have one, generally more than one, specific embodiment as well as a generalised concept. But there is no presumption that the patentee necessarily intended the widest possible meaning consistent with his purpose be given to the words that he used: purpose and meaning are different.
>
> (vi) Thus purpose is not the be-all and end-all. One is still at the end of the day concerned with the meaning of the language used. Hence the other extreme of the Protocol – a mere guideline – is also ruled out by Article 69 itself. It is the terms of the claims which delineate the patentee's territory.
>
> (vii) It follows that if the patentee has included what is obviously a deliberate limitation in his claims, it must have a meaning. One cannot disregard obviously intentional elements.
>
> (viii) It also follows that where a patentee has used a word or phrase which, acontextually, might have a particular meaning (narrow or wide) it does not necessarily have that meaning in context.
>
> (ix) It further follows that there is no general 'doctrine of equivalents.'

> (x) On the other hand purposive construction can lead to the conclusion that a technically trivial or minor difference between an element of a claim and the corresponding element of the alleged infringement nonetheless falls within the meaning of the element when read purposively. This is not because there is a doctrine of equivalents: it is because that is the fair way to read the claim in context.
>
> (xi) Finally purposive construction leads one to eschew the kind of meticulous verbal analysis which lawyers are too often tempted by their training to indulge."
>
> 19. Sub-paragraph (ix) must now be read in the light of the Supreme Court's judgment in *Actavis v Lilly* [2017] UKSC 48 , which explains that, at least when considering the scope of protection, there is now a second question, to be asked after the patent claim has been interpreted, which is designed to take account of equivalents. There was some reference in the written arguments to the impact of that decision on the present case. In the end, however, Mr Mellor disclaimed any reliance on any doctrine of equivalence for the purposes of supporting an expansive scope of claim in the context of invalidity. That issue will therefore have to await a case in which we are called upon to decide it.

200. There was also no dispute that a factor that may feed into claim construction is that a patentee is unlikely to have intended to cover prior art which is acknowledged in the specification. This may depend on the way it is acknowledged, however: see *Jushi v OCV* [2018] EWCA Civ 1416. This is because the skilled person has some appreciation of the purpose of a patent as defining something novel (and indeed of some other aspects of the patent system such as drafting conventions and the divisional system – I touch on that, which may be seen from *Virgin v Premium*, and some other more subtle points of the law of claim construction as I deal with the arguments below).

Law on reference to the file history

201. The law on when the court can have regard to the history of the patent's prosecution was set out in *Actavis UK Limited and ors v Eli Lilly & Co* [2017] UKSC 48 at [81] – [88]:

> 81. Actavis contends that the prosecution history, as summarised in paras 76 to 80 above, makes it clear that the claims of the Patent should be interpreted as being limited to pemetrexed disodium not only as a matter of language, but in the sense that the use of any other pemetrexed compound, including other pemetrexed salts and the free acid, could not infringe. This contention gives rise to two issues. The first is one of relatively general application, namely whether and if so when it is permissible to have recourse to the prosecution history of a patent when considering whether a variant infringes that patent. The second issue is whether the prosecution history of the Patent in this case alters the provisional conclusion reached in para 75 above.

82. So far as the first issue is concerned, Lord Hoffmann said *in Kirin-Amgen* [2005] RPC 9, para 35:

> "The courts of the United Kingdom, the Netherlands and Germany certainly discourage, if they do not actually prohibit, use of the patent office file in aid of construction. There are good reasons: the meaning of the patent should not change according to whether or not the person skilled in the art has access to the file and in any case life is too short for the limited assistance which it can provide. It is however frequently impossible to know without access, not merely to the file but to the private thoughts of the patentee and his advisors as well, what the reason was for some apparently inexplicable limitation in the extent of the monopoly claimed."

83. In the absence of good reason to the contrary, it would be wrong to depart from what was said by the House of Lords. It is said by Actavis that there is good reason to depart from what Lord Hoffmann said on the ground that he was wrong in his description of the German and Dutch approaches to this issue, and that anyway he failed to have regard to the jurisprudence of other European courts.

84. In my view, Lord Hoffmann was right about the approach of the German and Dutch courts to this issue. Thus, the Bundesgerichtshof, in a decision involving the German equivalent of the instant Patent, Case No X ZR 29/15 (*Eli Lilly v Actavis Group PTC*), paras 39-40, stated that "it is permissible … to use statements made by the applicant [and the examiner] during the grant procedure as an indication of how the person skilled in the art understands the subject matter of the patent" but "such indications cannot be readily used as the sole basis for construction". And in *Ciba-Geigy AG v Oté Optics BV* (1995) 28 IIC 748, the Dutch Supreme Court said that "a court will only be justified in using clarifying information from the public part of the granting file, when it holds that even after the average person skilled in the art has considered the description and the drawings, it is still open to question how the contents of the claims must be interpreted."

85. It is argued by Actavis that this limited approach to the circumstances in which reference can be made to the prosecution file may be more restrictive than the approach adopted in France, Italy, and Spain, as analysed by Arnold J. Thus, he said in para 162 of his judgment, that the Cour d'Appel observed in Case No 08/00882, *Hewlett Packard GmbH v Agilent Technologies Deutschland GmbH* (27 January 2010) that "the patentee who amended its clauses to give them a limited scope may not, without putting the safety of third parties at risk, claim that the amendments were not necessary, nor that the limited claims have the same scope as the broader claims". However, the court in that case had already decided on the natural meaning of the patent, and the contents of the file were merely being invoked to confirm the decision. The position in Italy, according to Arnold J in para 174 of his judgment, is that "there is no doctrine of prosecution history estoppel" and "there is no clear rule as to the relevance, if any, of the prosecution history as an aid to the

> interpretation of claims". In Spain there is a doctrine of *actos propios*, which as Arnold J explained in para 184, is "the doctrine of one's own acts", but it only justifies relying on the prosecution file in relation to statements which are "unequivocal, clear, precise, conclusive, undoubted and [do] not reflect any kind of ambiguity".
>
> 86. While the French courts appear to be more ready to refer to the prosecution file on issues of interpretation or scope than the German or Dutch courts, it is unclear how much, if any, difference there is in outcome. The position in relation to the Italian courts is more unclear, and it may well be that the effect of the approach of the Spanish courts is the same in outcome as that of the German and Dutch courts. In those circumstances, particularly as it may be inevitable that there is a degree of difference in the approach of different national courts on such an issue, there is nothing in the French, Italian, or Spanish jurisprudence which causes me to depart from the conclusion expressed by Lord Hoffmann.
>
> 87. In my judgment, it is appropriate for the UK courts to adopt a sceptical, but not absolutist, attitude to a suggestion that the contents of the prosecution file of a patent should be referred to when considering a question of interpretation or infringement, along substantially the same lines as the German and Dutch courts. It is tempting to exclude the file on the basis that anyone concerned about, or affected by, a patent should be entitled to rely on its contents without searching other records such as the prosecution file, as a matter of both principle and practicality. However, given that the contents of the file are publicly available (by virtue of article 128 EPC 2000) and (at least according to what we were told) are unlikely to be extensive, there will be occasions when justice may fairly be said to require reference to be made to the contents of the file. However, not least in the light of the wording of article 69 EPC 2000, which is discussed above, the circumstances in which a court can rely on the prosecution history to determine the extent of protection or scope of a patent must be limited.
>
> 88. While it would be arrogant to exclude the existence of any other circumstances, my current view is that reference to the file would only be appropriate where (i) the point at issue is truly unclear if one confines oneself to the specification and claims of the patent, and the contents of the file unambiguously resolve the point, or (ii) it would be contrary to the public interest for the contents of the file to be ignored. The first type of circumstance is, I hope, self-explanatory; the second would be exemplified by a case where the patentee had made it clear to the EPO that he was not seeking to contend that his patent, if granted, would extend its scope to the sort of variant which he now claims infringes.

202. I discussed the Supreme Court's conclusion regarding the use of patent prosecution history in *Siemens Gamesa v GE Energy* [2022] EWHC 3034 (Pat):

> 78. In my view these two paragraphs have to be read as a piece. The two possible circumstances referred to in [88] [in Actavis] as (i) and (ii) have to be read in the light of the scepticism expressed at the start of [87]; one

> expects that they will only rarely arise and that the conditions for them to do so will be stringent.
>
> 79. This is given effect as to (i) by the requirements that the point of interpretation has to be truly unclear and that the file unambiguously resolves the point. The first requirement will not be met merely because some point of interpretation is arguable both ways in the context of the specification; that happens all the time. More is needed. The second requires that the file provides a clear answer, and will not be met just because the file says something that might be relevant. It is not legitimate to promote the file into a sort of adjunct to the specification and of equal value with it.
>
> 80. As to (ii) the requirements are that the patentee made it clear that he was not seeking to extend the claims to the sort of variant said to infringe. Again, the mere fact that the file provides something that would have been of some potential relevance to claim scope had it been in the specification is not enough.
>
> 81. I record that Counsel for Siemens accepted that it is not only in relation to infringement by equivalence that the file may be relevant; it can also be relevant to normal, purposive infringement.
>
> 82. It was also common ground before me (based on *FibroGen v Akebia* [2020] EWHC 866 (Pat) and *Facebook v Voxer* [2021] EWHC 1377 (Pat)) that where claims have been amended the skilled person knows that, and the reason. This is a point about claim interpretation as such, bearing potentially on Actavis question 3, and distinct from reliance on the prosecution history, in particular because it does not open the door to what the patentee said (beyond that it was amending, and the reason in terms of the prior art necessitating it).

Alexion's main arguments

203. Alexion argued that the skilled person would see that SEQ ID NO: 4 had a leader sequence, which was not necessary to binding and perhaps also deleterious, and would not be regarded as part of a normal, final antibody because in the usual manufacturing approaches it would be cleaved off by the cellular machinery.

204. Alexion also argued that the purpose of the claim was the expression of a whole antibody that would bind C5. It said that the Defendants were ignoring purpose and focusing excessively on the normal meanings of "comprising" and "consisting". It said that it was not ignoring the "consisting" language (still less striking out the claim feature requiring SEQ ID NO: 4) but was simply making an argument as to what SEQ ID NO: 4 *meant*, purposively.

205. Alexion met the Defendants' point that the skilled person would not expect the claims to cover something old, namely eculizumab, by saying that the apparent acknowledgment in the Patent, at [0064], could be seen to be wrong by going back to Evans, which was incorporated by reference at [0133].

The Defendants' main arguments

206. The Defendants argued that "consisting" meant "having exactly" as a matter of drafting convention, that SEQ ID NO: 4 was clear and unambiguous in requiring exactly the sequence set out, including the leader sequence, that the skilled reader would think that the patentee was not intending to claim something old, and that while the usual methods of production would cleave the leader sequence that did not mean that it was not possible to make an antibody exactly as claimed, and that the skilled person would think that it *could* bind C5. They also said that Alexion's approach involved giving no meaning at all to a claim feature, which was not permitted as a matter of law.

Analysis – purposive construction

207. I will deal with purposive construction first and then consider the prosecution history separately.

208. The language actually used by the claims is of course a critical consideration. Here, the two most important features are that SEQ ID NO: 4 is a use of scientific language that would generally be expected to be precise, and the use of the drafting convention that "consisting of" specifies exactly what must be present. These matters are strongly in the Defendants' favour. I acknowledge that SEQ ID NO: 4 is referred to as "Eculizumab Light chain" and that this is not an entirely accurate description, but this does not really take matters forward for Alexion: it is common ground that the skilled reader would see that SEQ ID NO: 4 was the eculizumab light chain with a leader sequence of 22 extra amino acids.

209. Next, the skilled person would understand that the Patent was trying to claim something new. In case of doubt, they would lean away from a meaning which meant that the Patent covered something it said was old. What matters in relation to claim construction is working out the patentee's objectively determined intention. In the present case, the patentee said that eculizumab was old. This is only partly based on the reference to Evans in [0064], important though that is: the whole specification reads as if eculizumab was old and what was being contributed was new ways of using it. This also applies to all the "items" at [0135]: none of them is to eculizumab as such but rather to ways of using it.

210. I reject Alexion's reliance on the incorporation by reference of Evans at [0133]. It is just boiler plate and has the unrealistic effect of incorporating very large amounts of information willy-nilly into the Patent. In any event, even if one were to take account of it, the paragraph also says that in case of conflict the specification "will control", so the skilled person trying to understand and apply [0133] and who looked at [0064] and at Evans would think that they were being instructed to prefer the former over the latter.

211. It is also rather unrealistic for Alexion to assert that the skilled reader would think the Patent's claims were intended to cover eculizumab on the basis that it was new, when the specification does not say anywhere that it is new. It is a bootstraps argument for Alexion to argue that the reader would think that eculizumab was new because the claim would have been read as being intended to cover it. So for these reasons, although the skilled person would find that Evans did not in

fact disclose the full length eculizumab if they went to check, I do not accept that they would; they would take the patentee at its word and would anyway think that the patentee was treating eculizumab as old from the specification generally, quite apart from the Evans reference.

212. In addition, [0020] is a powerful point against Alexion because it specifies three things: eculizumab, pexelizumab, and an antibody with heavy chain SEQ ID NO: 2 and light chain SEQ ID NO: 4. The claims do not correspond to the first two but they do match the third. So this is a fairly plain case of what-is-not-claimed-is-disclaimed. Alexion's answer to this was that the antibody defined by reference to the SEQ IDs would be seen by the reader to be exactly the same as eculizumab, just being described twice, in different words. I think this is another bootstraps point (it assumes they are identical to try to reason that they are identical), and [0020] does not read that way at all, especially given the "In certain embodiments …In certain embodiments …. In certain embodiments …" language which implies they are different. It does not say or in any way imply that the two are the same and they are not even mentioned next to each other, rather being separated in the list by pexelizumab.

213. Alexion's main points in opening included whether it would make technical sense to claim an antibody which had the 22 additional amino acids; that such an antibody might not be capable of being made and/or might not bind C5. Surely, it said, it would be much more sensible to claim eculizumab which would be clearly understood to be capable of being made by routine means and which the specification demonstrated would bind C5?

214. However, Alexion conceded in its oral closing submissions that given the distance of the additional 22 amino acids, as a leader sequence, from the binding regions, the skilled person would have thought binding was *possible*. This is what Alexion had said to the TBA, as well. And although Counsel for Alexion was not willing to concede the point (because of litigation elsewhere, he explained) I accept Mr Buss' evidence that if the skilled person did want to make the antibody with the additional 22 amino acids, it could be done.

215. I also find that while the most normal methods of eukaryotic expression in cell lines such as CHO would have cleaved the leader sequence, those were not the only approaches available. This is consistent with [0074] of the Patent which says that monoclonal antibodies "may also" be produced in transfected cells such as CHO cells and NS0 cells (I was told that NS0 cells are another mammalian line). So the Patent does not teach that eukaryotic expression was essential.

216. So I conclude that the antibody with the additional 22 amino acids could be made and that it would not have been the skilled person's belief that it would not bind. What of the point that it would be more sensible to claim eculizumab?

217. I accept Alexion's argument that the skilled person would think eculizumab had greatly more obvious utility than an antibody with the additional 22 amino acids, and would scientifically be a much more natural thing to do if presented with the choice, but despite that I think there are two answers to the point.

218. The first is the point that the patentee had said that they regarded eculizumab as old, which I have already covered. It would just make no sense to claim something that would not be valid as a matter of patent law, even if it was scientifically more desirable.

219. The second answer is that even if the reader thought that the patentee had an interest in claiming eculizumab as such, that would not necessarily mean that it would be claimed in this patent. It might easily be claimed in another divisional in the same family (see *Virgin*, where a similar point arose, at [49]). Counsel for Alexion accepted this logic.

220. Moreover, this argument is not really about what the claim means at all; it is an argument about whether what it covers is the most technically desirable choice. Patents do sometimes claim things which are suboptimal or whose purpose is not entirely evident. That is not a licence to rewrite the claims.

Striking out a claim feature?

221. The Defendants argued that Alexion was trying to strike out a claim feature, the feature in question being the 22 amino acids at the start of SEQ ID NO: 4. I agree with Alexion that was not the nature of its argument. It accepted that the claim feature "consisting of SEQ ID NO: 4" had to have a meaning and a limiting effect on the claim's scope; its argument was about what that feature meant, purposively. But my rejection of this argument by the Defendants does not make any difference, because I reject the meaning advanced by Alexion for other reasons given above.

Skilled person's knowledge of the priority date

222. I was troubled earlier in the trial by the fact that the skilled person would struggle to understand what the patentee was trying to do: why was the patentee not claiming any of the facets of the TRIUMPH study, many of which are reflected in the "Items" at [0135]? Why, instead was the patentee trying to claim (on Alexion's construction) eculizumab itself, when the specification appeared to say it was old?

223. A large part of the explanation for this is, of course, the fact that the Patent is not entitled to priority so Hillmen 2006 was prior art. But the fact that the Patent is not entitled to priority does not appear from its face. However, the parties agreed that the skilled reader is to be taken to be told the date at which the claims' validity is to be assessed and I will proceed on that basis. So the skilled reader would know that Hillmen 2006 was prior art and that the methods and outcomes of the TRIUMPH study could not validly be claimed. This would dispel some of the possible confusion but in my view the skilled person would still think the patentee did not want to claim eculizumab as such, because it was old.

Excluding the literal meaning

224. I was also concerned at an earlier stage about whether, if Alexion's argument was correct, the Patent's claims would cover that which they literally referred to, an antibody with the 22 amino acid leader sequence, even if they purposively also

covered an antibody without it. How would that work given that Alexion had conceded invalidity if the Defendants were right about construction?

225. Alexion's response was that its purposive approach meant that the 22 amino acids were positively not to be present (not merely that they may not be) so the scenario that I asked about could not arise. It also said that its concession about invalidity was only made pragmatically because there was no point defending a claim that was not infringed. I am rather dubious about that since I think Alexion was constrained to accept invalidity on what it called the literal meaning given its approach that the antibody with the 22 amino acid leader sequence could not be made. In the event, though, I have rejected Alexion's purposive approach and found that the antibody with the 22 amino acid leader sequence could be made and might bind C5. So the argument does not seem to me to matter and I am really only mentioning it for completeness.

Prosecution history analysis

226. I can be quite brief about this. *Actavis v Lilly* allows reference to the prosecution history when the meaning of the claim is truly unclear and the contents of the file unambiguously resolves the point, or when it would be contrary to the public interest to ignore it, as when the patentee had made clear they were not seeking to extend the claims to the alleged infringement (I set out the full passage from Lord Neuberger above).

227. Neither side said that the Patent claims are ambiguous. To some extent this was of course merely presentational, since to say there was, or might be, an ambiguity could signal some lack of conviction in the primary argument. The Defendants did say that the claim either clearly meant what they said, or at best was ambiguous, but it was not the real thrust of their argument.

228. I do not think the claims are ambiguous. The situation is an odd one for a number of reasons that I have explored above but that does not mean the claim is ambiguous. Although I think the Defendants are right and have much the better of the argument there is at least something to be said for Alexion's position, but the fact that the meaning of the claim is debatable is not enough to make it sufficiently ambiguous to justify reference to the prosecution history, as I concluded in *Siemens Gamesa*.

229. Even if the claim were sufficiently ambiguous to justify looking to the prosecution file, I do not see how the file could "unambiguously resolve" the point. I found it hard to understand how the Defendants even contended that it might. The fact that Alexion tried and failed to get a claim which would literally cover eculizumab does not help understand the purposive meaning of the claims which it did get, although that provides a segue to the second aspect of *Actavis v Lilly*.

230. Lord Neuberger referred to a situation where the patentee makes clear in the prosecution file that it will not seek to extend the claims to the infringer's variant. In the present case, Alexion did no such thing. It sought a claim that would be literally infringed (precisely how it did this can be seen in the TBA decision but the details do not matter so I will not go into them here), but it made no argument

or concession about what would or would not infringe the claims it already had. Having been refused the claims that would have been literally infringed (for added matter) it now asserts that the granted claims are infringed on a purposive construction. It never said or intimated that it would not do that.

231. The present situation is exactly the same as in *Actavis v Lilly*, where the patentee sought a claim that would have literally been infringed by the potassium salt but was refused it, for added matter reasons. It was left with a claim to the sodium salt only, which was not literally infringed, but it was not prevented from making its argument, which succeeded, that there was infringement. It did so by way of equivalence rather than, as Alexion does here, under the banner of purposive construction, but that cannot make any difference. Counsel for the Defendants said that it did, but was unable to provide any reason why that should be so.

232. The Defendants sought to engage the public interest in a different way by drawing an analogy to *Akebia v Fibrogen* [2020] EWHC 866 (Pat), a decision of Arnold LJ (sitting at first instance), overturned on appeal although on other grounds. That was a quite different situation where (see [459]) the patentee had had to narrow the claims for reasons of substantive patentability (not added matter) but then was trying to run a claim construction at trial which would have the effect of recapturing the territory which had had to be excluded by the amendment.

233. Arnold LJ also earlier (453-454) said the situation arising from claim amendments in that case was an extreme instance of the principle from the decision of the Bundesgerichsthof in *Okklusionsvorrichtung*, Case X ZR 16/09 where only one of a number of possibilities disclosed in the specification is claimed; equivalents cannot then be used to cover the possibilities not claimed. I have had regard to a similar principle in this case arising from [0020] of the Patent, but not because of claim amendment and without any need to look to the prosecution history.

234. I note that the Defendants argued that novelty was assessed by the TBA on the basis of "an antibody as claimed" but they did not make good that the rejection of the anticipation arguments had anything to do with the 22 amino acids.

Claim 2 construction

235. Claim 2 requires a pharmaceutical composition comprising the antibody of claim 1.

236. The Defendants submitted that this required physical suitability as a pharmaceutical and not actual use as such, or any subjective intent to make such use.

237. I understood Alexion to accept this. The only place it matters is in relation to anticipation over Bowdish with Evans, where Alexion's points were about lack of clear disclosure of something suitable as a pharmaceutical and not about intention or actual use.

VALIDITY

238. I will set out the prior art citations (and Hillmen 2006) and then deal with the attacks over them. I set the citations out in a chronological fashion, but the Defendants' arguments group them in a variety of ways which cannot be conveyed in a linear fashion, e.g. because Thomas is invoked in both main attacks. I bear in mind that each must be read on its own and separately from the others, save where justified by a cross-reference, by a document being CGK, or (in the case of Thomas) on the basis that it would, the Defendants say, necessarily be found in the course of obvious research from another starting point.

Disclosure of Thomas

239. Thomas is an Alexion article published in 1996. I give its full title above under "The issues".

240. The start of the abstract states:

> **Abstract**- Activation of the complement system contributes significantly to the pathogenesis of numerous acute and chronic diseases. Recently, a monoclonal antibody (5G1.1) that recognizes the human complement protein C5, has been shown to effectively block C5 cleavage, thereby preventing the generation of the pro-inflammatory complement components C5a and C5b-9. Humanized 5G1.1 antibody, Fab and scFv molecules have been produced by grafting the complementarity determining regions of 5G1.1 on to human framework regions…

241. The Introduction states:

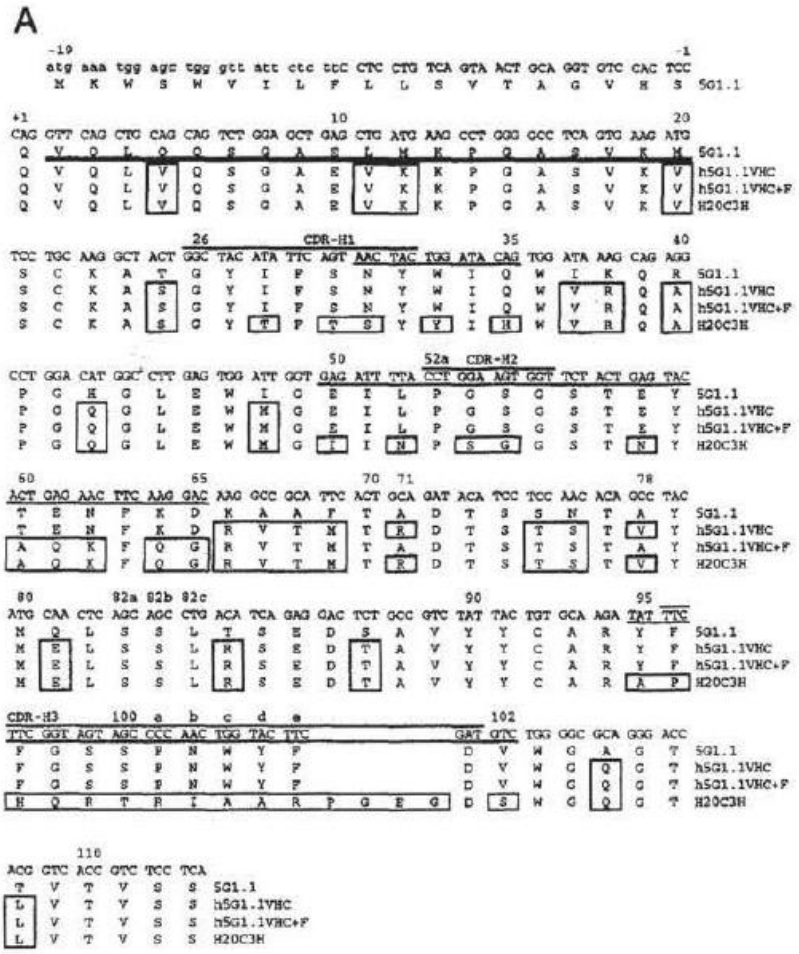
> …Development of a soluble form of complement receptor type 1 (sCR1), an inhibitor of C3 convertase activity, has provided a means to examine the potential of complement inhibition for the amelioration of several disease processes including xenotransplant rejection (Pruitt *et al*., 1994), lung and dermal immune complex-mediated injury (Mulligan *et al*., 1992), experimental allergic encephalomyelitis (Piddlesden *et al*., 1994), cardiopulmonary bypass (Moat *et al*., 1992; Gillinov *et al*., 1993) and reperfusion injury (Weisman *et al*., 1990; Smith *et al*., 1993: Pemberton *et al*., 1993). However, inhibition of the complement cascade by sCRI at the level of C3 convertase activity may be predicted to have significant clinical side effects. Generation of C3b is essential for the normal phagocytosis of bacterial and fungal pathogens as well as the clearance of circulating immune complexes (Liszewski and Atkinson, 1993). In fact, humans genetically deficient in C3 are subject to recurrent life-threatening infections and also suffer from a greatly increased incidence of autoimmune diseases such as systemic lupus erythematosus and glomerulonephritis (Ross and Densen, 1984).
>
> …
>
> In this study, variants of the 5G 1.1 monoclonal antibody have been engineered, which can be used in either acute or chronic settings. Firstly,

> the 5G 1.1 variable regions were humanized using the CDR-grafting technique (Riechmann et at., 1988). The humanized variable regions were then used to construct humanized antibody. Fab and scFv molecules which all maintained a high affinity for human C5 and blocked the generation of both C5a and C5b-9.

242. In the materials and methods section, the subheading "*humanization of 5G1.1 variable regions*" explains:

> Two humanized variants of the 5G 1.1 VL and VH regions were constructed by CDR grafting (Reichmann *et al*., 1988). For CDR grafting, the 5G1.1 heavy and light complementarity determining regions were introduced into the human heavy variable region H20C3H (Weng *et al*., 1992) to yield h5G1l1VHC (Fig. 1A) or the human light variable region I.23 (Klein *et al*., 1993) to yield h5G1.1VLC (Fig. 1B), respectively.

243. Figure 1 depicts the sequence of the 5G1.1 heavy (A) and light (B) variable regions:


A
B

244. Figure 1's description states:

> Fig. 1. Sequence of the 5G 1.1 heavy (A) and light (B) variable regions. The DNA sequence and the translated amino acid sequence of the cloned 5G1.1 variable regions are shown. Amino acid position is numbered according to *Kabat et al*. (1992), with the complementarity determining regions according to the hypervariable sequence definition (Kabat et al 1992) or the structural variability definition (Chothia and Lesk, 1987) underlined and overlined, respectively. Lower case letters indicate nucleotide sequences derived from primers used for cloning. Amino acid sequences obtained from protein sequencing are indicated by double underlines. The protein sequences of the human variable regions H20C3H and I.23 are shown below the appropriate 5G1.1 variable regions. h5G1.1 VHC and h5G1.1 VLC denote humanized heavy and light variable regions constructed by grafting the CDRs from 5G1.1 on to the H20C3H and I.23 human framework regions. The variable regions h5G1.1 VHC + F and h5G 1.1VLC+ F contain murine amino acids at framework positions 71 and 78 in the heavy variable region and position 71 in the light variable region in addition to the murine CDR sequences. Amino acids in the human variable regions and the humanized 5G1.1 variable regions which differ from the murine 5G1.1 sequences arc boxed.

245. In the results section, the sub-section "*humanization of 5G1.1*" describes the humanization as follows:

> For humanization, the 5G1.1 heavy variable regions CDRs were transposed into the human variable region H20C3H (Weng *et al*., 1992). This human V_H was derived from the human genomic VH gene HG3 (Rechavi *et al*., 1983), belonging to the V_{H1} family and the human genomic J_H5 gene, and contains no changes in the framework regions from these genomic genes. The 5G1.1 light variable region CDRs were grafted into the human light variable region I.23 (Klein *et al*., 1993). This human V_L region was derived from the human V_κl family gene O12 (Klein *et al*., 1993) and the genomic J_κl gene, with the introduction of an Arg residue in framework region 2 at position 38 in the I.23 cDNA as compared to the Gln residue encoded in the O12 genomic gene. Initial humanized 5G1.1 variable heavy and light regions were constructed by introducing the 5G1.1 CDRs into these human frameworks and are designated as h5G 1.1 VHC and 5Gl.l VLC (Fig. 1).

246. The sub-section "*construction of a humanized h5G1.1 antibody*" in the results section provides:

> Having demonstrated the effective humanization of the 5G1.1 variable regions, an intact humanized antibody (lgG4 isotype) was constructed and produced in 293- EBNA cells. The avidity of this humanized antibody (h5G1.1 HuG4) for human C5, was compared to the murine 5G1.1 mAb by determining the ability of each to compete binding of biotinylated 5G1.1 mAb to C5 (Fig. 9). The humanized h5G1.1 mAb had a two-fold lower avidity than the murine antibody. However, the humanized 5G1.1 HuG4 antibody was equipotent with the murine antibody at protecting

> PAEC from lysis by human serum, with a 0.5-fold molar ratio of antibody to C5 (1:1 ratio of antibody binding sites to C5) completely inhibiting lysis of the PAEC (Fig. 10).

247. The discussion section explains complement activation as follows:

> Complement activation has been suggested to be involved in the pathogenesis of several chronic human diseases including allograft rejection (reviewed by Baldwin *et al*. (1995)), systemic lupus erythematosus (reviewed by Mills (1994)), myasthenia gravis (reviewed by Drachman (1994)) and rheumatoid arthritis (reviewed by Morgan (1990)). Recently, it has been shown that prolonged treatment with an antibody to mouse C5 both blocks onset and disease progression in a collagen induced arthritis model (Wang *et al*., 1995), as well as inhibits development of glomerulonephritis in NZB/W mice (Wang *et al*., 1996). As the half-life of the h5G1.1scFv is likely to be too short to allow for chronic use in humans, a full length humanized antibody was also constructed. The human IgG4 isotype was chosen as this isotype does not activate human complement (Tao *et al*., 1993) and there is only one known allotype of lgG4 (Ghanem *et al*., 1988), precluding the potential development of allo-antibodies in patients. The humanized h5G1.1 (CDR) HuG4 antibody bound to human C5 with a similar avidity as the murine antibody when assayed by ELISA (Fig. 9) and inhibited lysis of porcine aortic endothelial cells as effectively as the murine antibody with a 1:1 molar ratio of antibody binding sites to human C5 being sufficient for inhibition (Fig. 10). Little information is available on the immunogenicity of CDR-grafted antibodies in humans. Repeated administration of chimeric antibodies containing intact murine variable regions, has induced an immune response directed against the murine variable regions in nearly all trials (reviewed in Khazaeli *et al*., (1994)). In this regard, it is significant that introduction of murine amino acids in the framework regions was not essential for maintenance of high affinity binding to C5. The h5G1.1 antibody is, therefore, likely to be minimally immunogenic in patients.

Disclosure of Evans

248. Evans is an Alexion patent application. Again, I give its full details above under "The issues".

249. The title is "C5-specific antibodies for the treatment of inflammatory diseases".

250. The field of the invention section states:

> The present invention relates to the treatment of glomerulonephritis (GN) and other inflammatory diseases, and more generally to therapeutic treatments involving the pharmacologic inhibition of a patient's complement system. In particular, the invention relates to the use of antibodies specific to human complement component C5 to accomplish such therapeutic treatment. The invention also relates to compositions comprising native monoclonal antibodies (mAbs) specific to human

> complement component C5 that block complement hemolytic activity and C5a generation at concentrations that substantially reach the theoretical one to two stoichiometric limit of antibody to antigen that can be achieved by a bivalent antibody. The invention further provides recombinant mabs that are derivatives (including monovalent derivatives) of these native mabs that provide substantially the same blocking activities as the native mabs.

251. The summary of the invention section, columns 7 – 8, states:

> …
>
> Although not wishing to be bound by any particular theory of operation, it is believed that the anti-C5 antibodies have these and other therapeutic effects through their activity in blocking the generation or activity of the C5a and/or C5b active fragments of complement component C5. Through this blocking effect, the antibodies inhibit the proinflammatory (anaphylatoxic) effects of C5a and the generation of the C5b-9 membrane attack complex (MAC). Significantly, the blockage effected by the anti-C5 antibodies, since it occurs at the level of complement component C5, has the advantage of maintaining important opsonic, anti-infective, and immune complex clearance functions of the complement system mediated by, inter alia, complement component C3.
>
> …
>
> Although other antibodies can be used to treat GN in accordance with the present invention, the novel antibodies of the invention are preferred. Preferably, these novel antibodies bind to the alpha chain of C5, but do not exhibit substantial binding to the alpha chain cleavage product C5a (referred to hereinafter and in the claims as “free C5a”). Other preferred targets for antibody binding include fragments of the alpha chain of human C5 that are immunoreactive with the most preferred antibody of the invention, the 5G1.1 antibody discussed below. Such preferred targets include the 46 kDa acid hydrolysis fragment of C5 (the "5G46k” fragment), the 27 kDa tryptic digestion fragment of C5 (the “5G27k” fragment), the 325aa peptide spanning amino acid residues 725-1049 of SEQ ID NO:2 (the "5G325aa” peptide), the 200 amino acid peptide spanning amino acids residues 850 to 1049 of SEQ ID NO:2 (the "5G200aa” peptide)-as discussed below in Example 13.
>
> The novel antibodies of the invention include antibodies that bind to an epitope within the amino acid sequence Val Ile Asp His Gln Gly Thr Lys Ser Ser Lys Cys Val Arg Gln Lys Val Glu Gly Ser Ser, (SEQ ID NO:1) hereinafter referred to as the KSSKC epitope. These novel antibodies that bind to the KSSKC epitope (SEQ ID NO: 1) are hereinafter referred to as anti-KSSKC antibodies, and monoclonal antibodies binding to the KSSKC epitope are hereinafter referred to as anti-KSSKC mAbs.
>
> …

> Particularly preferred antibodies of the invention are monospecific native anti-KSSKC antibodies. The 5G1.1 native anti-KSSKC mAb has the distinct advantage of substantially blocking both complement hemolytic activity and the generation of C5a at a stoichiometric ratio of antibody to C5 that approaches the theoretical one to two (antibody to antigen) limit of binding that can be achieved by a bivalent antibody. This is a desirable property because it allows smaller doses of antibody to achieve therapeutic effects than would be required of otherwise similar antibodies that cannot function at such a ratio.

252. Columns 9 – 10 in the brief description of the drawing section state:

> …
>
> FIG. 18. The light chain variable region of the antibody 5G1.1. Sequence derived from the 5' oligonucleotide primer used for PCR amplification of the variable region is shown in lower case. Amino acids are number according to Kabat et al., supra. Boxed amino acids correspond to peptide sequences obtained from the mature 5G1.1 light chain or from an endoproteinase Lys C peptide of 5G1.1. The complementarity determining region (CDR) residues according to the sequence variability definition and the structural variability definition are underlined and overlined, respectively.
>
> FIG. 19. The heavy chain variable region of the antibody 5G1.1. sequence derived from the 5' oligonucleotide primer used for PCR amplification of the variable region is shown in lower case. Amino acids are numbered using the scheme of Kabat et al. supra with +1 denoting the first amino acid of the processed mature variable region. Boxed amino acids correspond to peptide sequence obtained from the 5G1.1 heavy chain after treatment with pyroglutamate aminopeptidase. The complementarity determining region (CDR) residues according to the sequence variability definition or according to the structural variability definition are under lined and overlined, respectively.

253. Figure 19 is as follows:

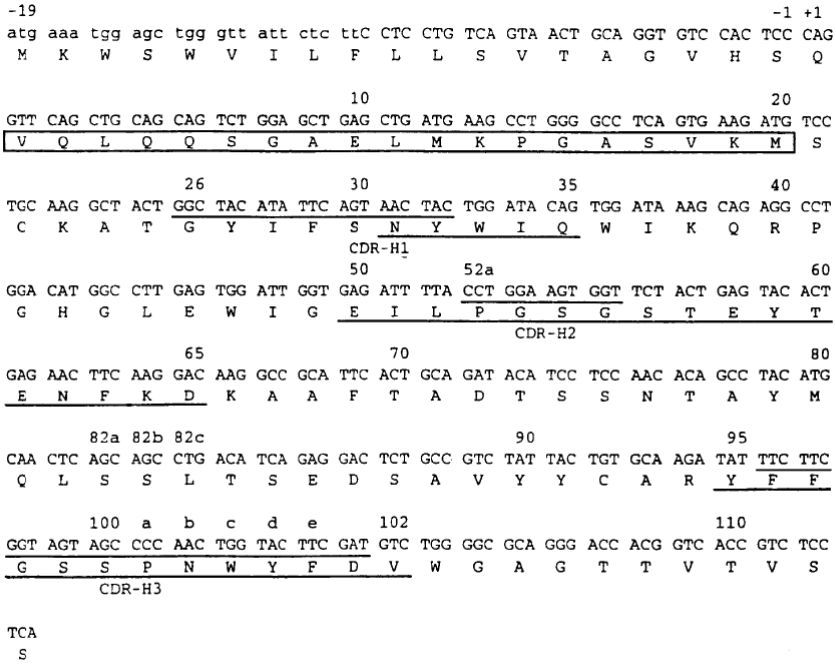


FIG.19

254. The background and physiology & pathology section, column 17, states:

> Anti-C5 mabs that have the desirable ability to block complement hemolytic activity and to block the generation of C5a (and are thus preferred for use in the treatment of GN and other inflammatory conditions in accordance with the present invention) have been known in the art since at least 1982 (Moongkarndi et al. Immunobiol. 1982, 162:397; Moongkarndi et al. Immunobiol. 1983, 165:323). Antibodies known in the art that are immunoreactive against C5 or C5 fragments include antibodies against the C5 beta chain (Moongkarndi et al. Immunobiol. 1982, 162:397; Moongkarndi et al. Immunobiol. 1983, 165:323; Wurzner et al. 1991, Supra; Mollnes et al. Scand. J. Immunol. 1988, 28:307-312); C5a (see for example, Ames et al. J. Immunol. 1994, 152:4572–4581, U.S. Pat. No. 4,686,100, and European patent publication No. 0 411306); and antibodies against non-human C5 (see for example, Giclas et al. J. Immunol. Meth. 1987, 105:201-209). Significantly, none of these anti-C5 mAbs has the properties of the novel anti-C5 mabs of the invention, i.e., none of them binds to the C5 alpha chain but not to the C5 cleavage product C5a, none of them has the ability to substantially block both complement hemolytic activity and the generation of C5a to Substantially the same extent at the Same concentration of antibody. It is noteworthy that an scFv derivative of the N19/8 antibody of Wurzner et al. 1991, Supra, has been prepared, and that the N19/8 scFv has 50% less inhibitory activity towards C5a generation than the native N19/8 antibody (see Example 15). This is in contrast to the 5G1.1 scFv, which retained substantially all of its inhibitory towards C5a generation (see Example 12).

255. Example 11 in the examples section provides:

> Construction and Expression of Recombinant mAbs
>
> Recombinant DNA constructions encoding the recombinant mAbs comprising the 5G1.1 CDRs are prepared by conventional recombinant DNA methods including restriction fragment subcloning and overlapping PCR procedures. The resulting recombinant mAb-encoding DNAs include:
>
> > (1) one encoding a non-humanized (murine) scFv designated 5G1.1M1scFv (SEQ ID NO:7), wherein CDRL1 is amino acid residues 28–34 of SEQ ID NO:7, CDRL2 is amino acid residues 52-54 of SEQ ID NO:7, CDR L3 is amino acid residues 93–98 of SEQ ID NO:7, CDR H1 is amino acid residues 156-159 of SEQ ID NO:7, CDR H2 is amino acid residues 179-183 of SEQ ID NO:7, and CDR H3 is amino acid residues 226–236 of SEQ ID NO:7;
> >
> > …
> >
> > (5) one encoding a humanized (CDR grafted and framework sequence altered) Fd designated 5G1.1 VH+IGHRL (SEQ ID NO:11), wherein CDR H1 is amino acid residues 26–35 of SEQID NO:11, CDR H2 is amino acid residues 50-60 of SEQ ID NO:11, and CDR H3 is amino acid residues 99-111 of SEQ ID NO:11;
> >
> > (6) one encoding a humanized (CDR grafted, not framework altered) Fd designated 5G1.1 VH+IGHRLC (SEQ ID NO:12), CDR H1 is amino acid residues 26–35 of SEQ ID NO:12, CDR H2 is amino acid residues 50–66 of SEQ ID NO:12, and CDR H3 is amino acid residues 99-111 of SEQ ID NO:12;
> >
> > …
>
> In accordance with the invention, matched pairs of the variable regions (e.g., a VL and a VH region) of the various antibody molecules, Fds, and light chains described above may be combined with constant region domains by recombinant DNA or other methods known in the art to form full length antibodies of the invention. Particularly preferred constant regions for this purpose are IgG constant regions, which may be unaltered, or constructed of a mixture of constant domains from IgGs of various subtypes, e.g., IgG1 and IgG 4.

256. Example 12, column 50 states:

> Additionally, these data demonstrate that the m5G1.1 scFv retained similar activity to that of the parent molecule (the native murine 5G1.1 mAb) in that the molar concentration of 5G1.1 murine scFv required to completely block C5a and C5b-9 (0.15 μM) was within two-fold of that required for the 5G1.1 mAb and Fab (0.06–0.08 μM).

Disclosure of Mueller

257. Mueller is an Alexion article from 1997; once again details of the title and publication appear above.

258. The introduction states:

> …
>
> The stable adhesion of lymphocytes, natural killer cells, and monocytes to endothelial cells is mediated predominantly by the interaction of the integrins LFA-1 (CD11a/CD18) and VLA-4 (CD49d/CD29) with their cognate ligands ICAM-1 and VCAM-1 on endothelial cells (Allavena *et al*., 1991; Jonjic *et al*., 1992). For both monocytes (Luscinskas *et al*., 1994) and T lymphocytes (Alon *et al*., 1995; Luscinskas *et al*., 1995) the binding of VLA-4 to VCAM is an essential component of the *in vitro* adhesive interactions required for stable arrest under conditions of flow.
>
> …
>
> Here we have utilized antibody engineering strategies to create humanized anti-porcine VCAM antibodies that block adhesion of human natural killer cells, monocytes, and T lymphocytes to activated PAEC. Furthermore, we show the choice of human isotype has critical implications for the potential therapeutic use of humanized antibodies in xenotransplantation.

259. The subsection, "*Identification of porcine VCAM domains recognized by blocking* mAbs" in the "results" section states:

> Previously, we have identified two murine mAbs (3F4 and 2A2) directed against porcine VCAM (pVCAM) which block VLA-4 dependent adhesion of peripheral blood human T cells to PAEC. These two mAbs are specific for pVCAM and do not recognize human VCAM (hVCAM). Here an initial analysis of the epitope specificity of the 2A2 and 3F4 mAbs was performed using fusion proteins consisting of various domains of pVCAM or hVCAM joined to the Fc region of human IgG l. The VCAM/ Ig fusion proteins were produced in 293-EBNA cells and assayed for binding of 2A2 and 3F4 mAbs by ELISA (Fig. 1). Both the 2A2 and 3F4 mAbs bound efficiently to proteins containing the first three domains of pVCAM. The 2A2 mAb bound to fusion proteins containing pVCAM domain 1 such as pDl + pD2 (porcine domain 1 plus porcine domain 2) and pDl + hD2 (porcine domain I plus human domain 2), but did not bind to fusion proteins lacking pVCAM domain I such as pD2 + pD3, hD 1+ pD2, or hD 1+ hD2.

260. The subsection "*inhibition of human leukocyte binding to PAEC by chimeric anti-porcine VCAM mAbs*" states:

> …

> These problems have been significantly reduced by the use of chimeric antibodies consisting of the murine variable regions joined to human constant regions (Khazaeli *et al*., 1994). To create anti-pVCAM chimeric antibodies we cloned the variable regions from both 2A2 and 3F4. The murine variable heavy regions were joined to the human IgG4 constant region (HuG4) since this isotype does not activate complement (C) (Tao *et al*., 1993), the predominant mediator of hyperacute rejection of xenografts.
>
> …
>
> The ability of the ch2A2 HuG4 and ch3F4 HuG4 mAbs to inhibit binding of cells expressing both VLA-4 and LFA-1 was next examined using the Jurkat T cell line. Both the ch2A2 HuG4 and ch3F4 HuG4 antibodies inhibited the binding of Jurkat to activated PAEC by up to 90% while the control antibody h5Gl.l HuG4 did not inhibit binding at any concentration (Fig. 4(A)). Similarly, the ch2A2 HuG4 and ch3F4 HuG4 antibodies inhibited the binding of both resting (Fig. 4(B)) and activated (Fig. 4(C)) T cells to activated PAEC, although the maximal inhibition achieved was reduced to approximately 60%...
>
> The potential of the ch2A2 HuG4 and ch3F4 HuG4 antibodies to inhibit binding of natural killer cells and monocytes to activated PAEC was examined using the cell lines YT (Yodio *et al*., 1985) and U-937 (Sundstron and Nilsson, 1976), respectively. Binding of YT cells to activated PAEC was strongly inhibited by concentrations of 10 µg/ml ch2A2 HuG4 and ch3F4 HuG4 antibodies (Fig. 5(A)). In contrast, the ch2A2 HuG4 and ch3F4 HuG4 antibodies did not inhibit binding of U-937 cells to activated PAEC (Fig. 5(B)). One possible explanation for this failure to inhibit U-937 cell binding could be the presence of elevated levels of VLA-4 on U-937 cells. However, FACS analysis revealed the presence of comparable levels of CD49d and activated CD29 on U-937 cells as on other cell lines such as Jurkat whose adhesion to PAEC was inhibited by the chimeric anti-pVCAM antibodies (Fig. 6). Interestingly, the adhesion of U-937 to PAEC was consistently augmented by approximately 50% in all experiments. This increase was specific for the anti-pVCAM antibodies as no increase in U-937 binding to PAEC was detected in the presence of the control h5G 1.1 H uG4 antibody (Fig. 5(B)). This suggested that binding of U-937 to PAEC could be increased through FcR binding to the anti-pVCAM HuG4 antibodies on the PAEC surface. In support of this hypothesis, FACS analysis confirmed the presence of significant levels of FcγRI (CD64), FcyRII (CD32) and FcyRIII (CDI6) on the surface of U-937 cells. In contrast, Jurkat and YT cells had no detectable Fcy receptors while Ramos cells showed the presence of only low levels of FcyRII (Fig. 6).
>
> Binding of the HuG4 chimeric antibodies to U-937 could be directly demonstrated by flow cytometry (Fig. 7). …

261. The subsection "*Inhibition of FcR binding of humanized mAbs with altered constant regions*" states:

…

The use of intact antibodies with human constant regions as anti-rejection agents is complicated by the capacity or such antibodies to fix C and for to bind FcRs. Human antibodies of the G4 isotype are devoid of C activity (Tao *et al*., 1993; Smith *et al*., 1995). Human antibodies of the G2 isotype do not activate C or bind FcRs (Canfield and Morrison, 1991; Burton and Woof, 1992). Rather than altering the specific residues known to mediate C fixation and FcR binding, we explored the possibility of creating an antibody with a composite human constant region. To create chimeric mAbs which would not activate C or bind to FcRs, we utilized the overall similarity in the human G2 and G4 primary sequences to design a HuG2/G4 composite antibody consisting of the first constant region domain and the hinge region from the HuG2 isotype joined to the second and third constant region domains from the HuG4 isotypes (Fig. 9).

262. Figure 9 and its description are as follows:

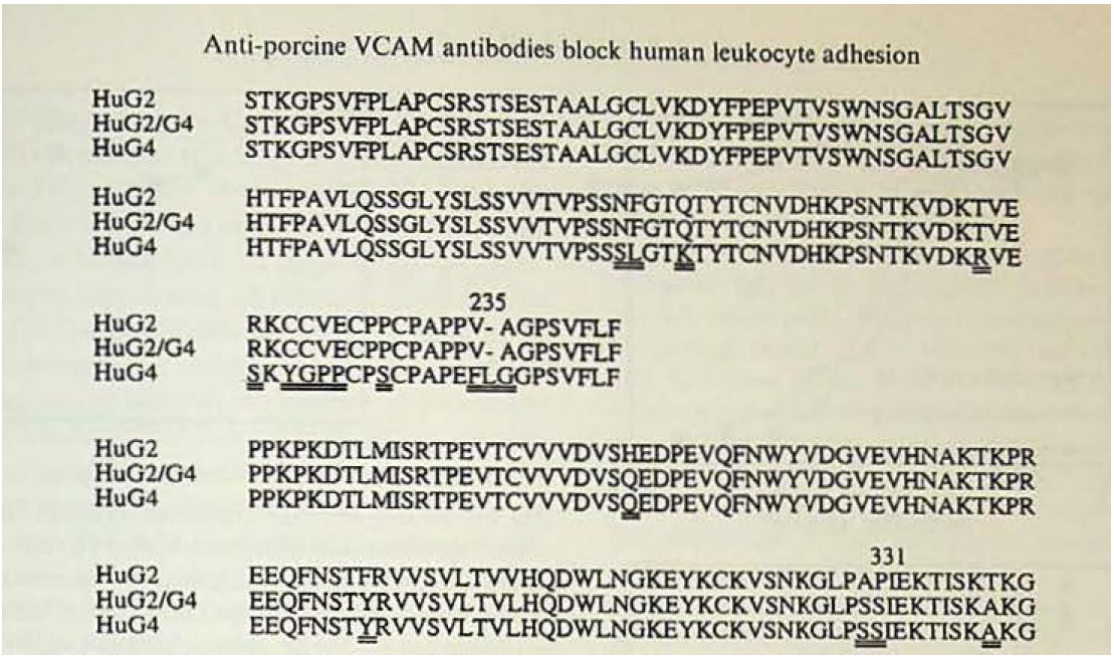


Fig. 9. Sequence of the CH1, hinge and CH2 regions of human lgG2 (HuG2), human lgG4 (HuG4), and the chimeric HuG2/G4 construct. Positions where differences occur between the three molecules are double underlined. The amino acid sequence at position 235/236 determines ability to bind to Fc*g* receptors (Canfield and Morrison, 1991 ; Duncan *et al*., 1988; Alegre *et al*., 1992; Burton and Woof, 1992) while the presence of a serine at position 331 confers the inability to activate C (Tao *et al*., 1993).

263. The discussion section explains:

…In either case the resulting human IgG4 constant region contains amino acid differences which could be immunogenic. Here, we have created chimeric antibodies (designated HuG2/G4) containing the CH 1 domain

> and hinge linker region of human IgG2 followed by the CH2 and CH3 domains of the human IgG4 constant region.

Disclosure of Bowdish

264. Bowdish is a patent application entitled "Rationally designed antibodies" with a filing date of 2 December 2002 and a publication date of 18 December 2003.

265. In the "Technical field" section, paragraph [0004] states:

> …Peptide epitopes and mimotopes due to their small size are potentially advantageous over large protein molecules for use as therapeutic reagents. However, the results with these peptides as therapeutics may often be unsatisfactory. One drawback to the use of peptides as therapeutic reagents is that they are generally unstable in vivo, i.e., their clearance rates from serum may be quite rapid. In addition, it is difficult to predict the activity, therapeutic or otherwise, of a peptide if it is fused into a larger molecule since conformational changes and other molecular forces may interfere with or totally negate the activity of the peptide. … Therefore, it is an object herein to provide rationally designed antibodies or fragments thereof which include biologically active peptides for use as diagnostic and therapeutic reagents.

266. Paragraph [0005], in the "Summary" section is as follows:

> Provided herein are biologically active recombinant antibodies and fragments thereof that mimic the activity of biologically active peptides, methods of making such antibodies and methods for their use in therapy and diagnosis. These antibodies and fragments thereof do not suffer from some of the disadvantages of isolated peptides, as antibodies naturally have long serum half-lives and are highly specific in binding their target. It has surprisingly been found that incorporation of particular amino acids surrounding a target peptide that has been combined into an antibody molecule actually increases the biological activity of the peptide.

267. In the "Detailed description" section, paragraph [0066] states:

> [0066] Any antibody can serve as a scaffold sequence, however typically human antibodies are chosen as human therapeutics is one of the ultimate objectives. Human or humanized antibodies are less likely to cause an adverse immune response in a human patient. The major criteria in selecting an antibody to serve as a framework for insertion of a peptide, is that the replacement of one or more CDRs of the antibody with the peptide must change the antigen specificity. The antibody can be a complete antibody or an Fab, scFv or $F(ab')_2$ fragment or portion thereof.

268. Paragraphs [0162], [0165] – [0167], [0170] and [0172] in "Example 1" provide:

> [0162] An agonist TPO mimetic-peptide IEGPTLRQWLAARA (SEQ. ID. NO: 1) was grafted into the anti-tetanus toxoid (TT) Fab heavy chain CDR3 (HCDR3), replacing the entire HCDR3 sequence

GDTIFGVTMGYYAMDV (SEQ. ID. NO: 4). **FIG. 2A** shows the sequence for the human tetanus toxoid antibody employed. Two grafting approaches were taken. In the first approach the agonist peptide was inserted into the H-CDR3 region with two glycines flanking each side. This was to reduce structural constraints on the grafted peptide so that it could more easily adopt the needed conformation. In the second approach, two amino acid positions on each side of the peptide graft were randomized in order that the best presentation of the peptide could be achieved (**FIG. 3**).

…

[0165] Selection of the TPO Mimetic Peptide Heavy Chain CDR3 Library

[0166] In order to select for the optimal peptide display, panning was performed on human platelets. Because platelets express approximately 1800 TPO receptors per cell on their surface (cMpl receptors), they represented a good cell target. In addition, platelets are readily available from a local Blood Bank. To 1 ml of concentrated indated human platelets from the Blood Bank, 50 uls of freshly prepared Fab-phage were added in a 15 ml conical tube with 0.1% NaN3. The tube was mixed at room temperature for 1-2 hours. Typically, 10 mls of 50% human serum (taken off the remaining platelets)+50%{IMDM/10% FBS/0.1% azide/2 mM EDTA} was added to the phage/cells. Platelets were pelleted at 5500xg for 5 minutes at room temperature. Supernatant was drained and the pellet was left resting under -500 uls of the wash for 20 minutes. The platelets were very gently resuspended and then 10 mls of 25% human serum (taken off the remaining platelets)+ 75%{IMDM/10% FBS/ 0.1% azide/2 mM EDTA} was added to the phage/cells. The centrifugation, pellet rest, and resuspension of the platelets was repeated. In panning rounds 3 and 4, a third wash was performed. The washed phage/cells were transferred to an eppindorf tube and spun at 5200xg. Phage were eluted from the platelets 10 minutes at room temperature using acid elution buffer (0.1 M HCl, 1 mg/ml BSA, and glycine to pH 2.2). Platelets were pelleted at max speed and the eluted phage transferred to a 50 ml conical tube, neutralized with 2M Tris Base. Phage were then allowed to infect fresh ER2537 bacteria for 15 minutes at room temperature and amplified overnight as described above. Four rounds of platelet panning were performed.

[0167] After the fourth round of panning, pools of 3 Fab clones expressed as soluble proteins in nonsuppressor bacterial strain TOP10F' (Invitrogen, Carlsbad, Calif.) were tested by Facs for binding to platelets by utilizing the Fabs' HA epitope tag with rat high affinity anti-HA followed by anti-Rat-FITC (Sigma, St. Louis, Mo.). 25 uls indated concentrated human platelets (washed once with PBS/5 mM EDTA/2% FBS) were incubated with 100 µls bacterial supernate (60 uls bacterial supernate from three pooled Fab clones were pre-incubated with 40 uls 5% Milk/PSS at 4º for 15 minutes) at room temperature for 20-30 minutes. 1 ml of FACS buffer (PBS/2% FBS/5 mM EDTA) was added and cells spun down at 5200xg for 5 minutes. Pelleted cells were resuspended in 50 uls of I: 10 diluted (in PBS/1% BSA/0.1% NaN3) 2° anti-HA antibody [Rat IgG anti-HA High

Affinity clone 3F10 (Roche Molecular Biochemicals)] was added. After 30 minutes at room temperature, the cells were washed with 1 ml FACS buffer as above. Following centrifugation, cells were resuspended in 100 uls of 1:160 diluted (in PBS/1% BSA/0.1% NaN_3) 3° anti-Rat IgG-FITC antibody (Sigma) and incubated 20 minutes at room temperature in the dark. Cells were washed with 1 ml FACS buffer then resuspended in 200 uls FACS buffer for analysis. As a positive control a commercially available sheep anti-lib/IIIaAb followed by anti-sheep FITC was used. Many pools of Fabs were clearly positive for binding to platelets by Facs. Follow up Facs analysis was then performed to identify individual clones that bound to the platelets.

…

[0170] To further examine the binding capabilities of Fabs, Facs analysis was performed on CMK cells, a Megakaryocytic cell line (from German Collection of Microorganisms and Cell Cultures) which also expresses the cMpl receptor. Fab clones that bound CMK cells were then analyzed to verify that the platelet and CMK cell binding was occurring via the cMpl receptor. For that experiment, 293 EBNA cells were transfected with or without the cMpl-R, which had been cloned from Tf-1 cells by RT-PCR. $1x10^6$ transfected cells were incubated with bacterial supernate from each Fab clone (pre-blocked as described above) for 20-30 minutes at room temperature. Cells were spun down at 2000 rpm for 5 minutes. Pelleted cells were resuspended in 90 µls FACS buffer (PBS/2% FBS/1 mM EDTA) then 10 uls of 2° anti-HA antibody [Rat IgG anti-HA High Affinity clone 3F10 (Boehringer Mannheim Biochemicals) was added for a final1:10 dilution. After 20 minutes at room temperature, the cells were washed with 1 ml FACS buffer. Following centrifugation, cells were resuspended in 100 uls of 1:50 diluted (in PBS/1% BSA/0.1% NaN3) 3° anti-Rat IgG-PE antibody (Research Diagnostics Incorporated, RDI) and incubated 20 minutes at room temperature in the dark. Cells were washed with 1 ml FACS buffer then resuspended in 200 µls FACS buffer for analysis. Fabs selected during panning demonstrated strong binding to cells transfected with the cMpl-R but not to control vector transfected cells lacking the cMpl-R. This indicates that cell surface binding was occurring specifically through the cMpl receptor. Anti-TT Fab does not bind to control vector or cMpl-R transfected 293 cells. However, Fab clone X1c shows a shift from 3% binding of control (non-cMpl receptor) transfected cells to 95% binding of cells expressing the cMpl-R.

…

[0172] Sequence analysis of Fab clones which specifically bound to the cMpl receptor (see **FIG. 5**), revealed the selection of preferred amino acids at the downstream linkage site. The DNA sequence data was analyzed and the amino acid and DNA sequences are as follows:

Clone	Binding Properties	SEQ. ID. NO	Sequence
X1a	weak	25	Pro Pro (14 aa peptide) Gly Gly
X1a-11	weak	27	Gly Gly (14 aa peptide) Gly Gly
X1a-13	weak	29	Gly Gly (14 aa peptide) Gly Gly
X1c	strong	31	Trp Leu (14 aa peptide) Pro Val
X2c	weak	33	Met Ile (14 aa peptide*) Val Gly
X3a	strong	35	Val Val (14 aa peptide) Pro Val
X3b	strong	37	Gly Pro (14 aa peptide) Pro Asp
X4b	strong	39	Leu Pro (14 aa peptide) Pro Val
X4c	strong	41	Ser Leu (14 aa peptide) Pro Ile
X5a	strong	43	Thr Met (14 aa peptide) Pro Val
X5c	strong	45	Trp Leu (14 aa peptide) Pro-Val
X7a	weak	47	Thr Arg (14 aa peptide*) Cys Ser
X7b	weak		deletion mutant this clone has lost the peptide
X7c	strong	49	Gln Thr (14 aa peptide) Pro Asp

269. In "Example 4", paragraphs [0191] – [0193] state:

> [0191] The TPO mimetic peptide graft in Fab clone X4b has been transplanted into the heavy chain CDR3 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. The sequence was cloned into 5G1.1 in such a fashion as to replace the native CDR3 with 5' ttg cca ATT GAA GGG CCG ACG CTG CGG CAA TGG CTG GCG GCG CGC GCG cct gtt 3' (SEQ. ID. NO: 65). The peptide graft translated into amino acids is Leu Pro Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala Pro Val (SEQ. ID. NO: 66). The 5G1+peptide was produced as a whole IgG antibody (See **FIGS. 13A and 13B**).
>
> [0192] Purified 5G1.1+peptide antibody as well as the parental 5G1.1 were analyzed for their ability to bind to cMpl receptor by FACS analysis. Binding to receptor expressing and non-receptor expressing 293 cells was compared. See **FIG. 14**. The FACS staining was performed essentially as described previously herein, with the exception that the detection was done using PE conjugated F(ab')2 fragment of goat anti-human IgG (H+L). The negative controls of 3° only anti-tetanus toxoid irrelevant Fab, and Fab X1a which binds weakly to cMpl receptor all showed very little staining. However, binding Fabs X1c and X4b showed strong staining as did the 5G1.1+peptide. None of those clones demonstrated binding to the non-receptor expressing cells indicating that the cell staining is occurring through specific recognition of the cMpl receptor. The parental 5G1.1 without the TPO mimetic peptide did not show staining to any of the cells tested.
>
> [0193] The ability of the 5G1.1 +peptide whole IgG to activate the cMpl receptor using the luciferase reporter assay has been determined (see **FIG.**

15). The results herein indicate that the configuration of a whole IgG causes steric limitations in its ability to productively bring the two cMpl receptors together for activation. The activity of the 5G1.1 full IgG construct containing the TPO mimetic peptide in the heavy chain CDR3 positions, was only weakly activating and required approximately 100-200 fold higher molar concentrations as compared to TPO, to stimulate equivalent activity. As was previously observed with the binding experiments, activation by the 5G1.1 containing the peptide was observed only when the cMpl-R was expressed on the cell surface. No receptor specific binding or activity was observed with the parental 5G1.1 not containing the peptide. These results demonstrate that binding and activity of the TPO mimetic peptide and selected amino acid flanking sequences is not limited to or specific for the Tetanus Toxoid antibody framework, but can be applied to other antibody frameworks. Thus the flanking amino acid sequences that were selected during panning are specific for presentation of the TPO mimetic peptide within a given CDR position, but not for amino acid sequence of the antibody framework.

270. Figure 13A "depicts the amino acid sequence and nucleic acid sequence of the 5G1.1-TPO heavy chain (SEQ. ID. NOS: 67 and 68, respectively)". Figure 13B "depicts the amino acid sequence and nucleic acid sequence of the 5G1.1 light chain (SEQ. ID. NOS: 69, and 70, respectively)".

271. Figure 14 "is a bar graph showing FACS analysis of cMpl receptor binding of purified 5G1.1+ TPO mimetic peptide compared to parental 5G1.1 antibody":

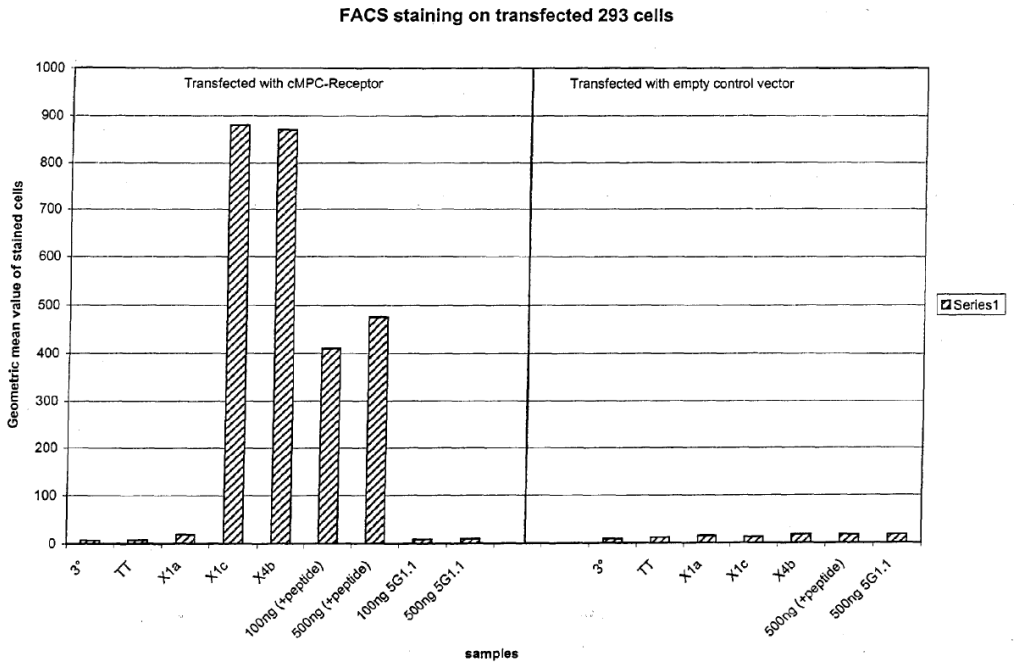


Fig. 14

Disclosure of Tacken

272. Tacken is another Alexion article and, again, full details including its title appear above.

273. In the "Patients, materials, and methods" section, the subsection "Recombinant antibodies" explains:

> The humanized antihuman DC-SIGN antibody hD1V1G2/G4 (hD1) was generated by complementarity determining region (CDR) grafting of AZN-D1 hypervariable domains into human framework regions. The humanized variable heavy and variable light regions were then genetically fused with a human hybrid IgG2/IgG4 constant domain[17] and a human kappa chain constant domain, respectively. This construct was cloned into a mammalian expression vector and the final construct transfected into NSO cells. Stable transfectants were obtained using glutamate synthetase (GS) selection (Lonza Biologics, Portsmouth, NH). Supernatants containing hD1 were purified over a protein A column. An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[19]

274. The "Binding and internalization assays" subsection also explains:

> Binding of hD1 and hD1-KLH to iDCs was assessed by immunofluorescence and flow cytometry. iDCs were incubated with or without 10 μg/mL hD1 or hD1-KLH. In some experiments, DC-SIGN was blocked by pretreating iDCs with 100 μg/mL AZN-D1. After a one-hour incubation at 4°C, cells were washed and incubated with Alexa Fluor 647–labelled anti–human IgG antibody. Cells were analyzed on a FACSCalibur flow cytometer using CellQuest software (BD Biosciences, San Jose, CA). Internalization of hD1 by iDCs was determined by flow cytometry as described previously.[24] Briefly, iDCs were incubated with 10 μg/mL hD1, AZN-D1, AZN-L19, or mouse IgG1 and 5G1.1 isotype control antibodies at 4°C for 30 minutes, washed, and incubated for 0, 15, 30, or 45 minutes at 37°C. Subsequently, some of the cells were fixed, while others were fixed and permeabilized in PBS/0.1% (vol/wt) saponin (Sigma-Aldrich) before addition of the Alexa Fluor 647–labeled anti–human IgG secondary antibody. The amount of internalized antibody was calculated by subtracting the mean fluorescence in fixed cells (surface bound) from that recorded with fixed and permeabilized cells (internalized and surface bound) at the various time points.
>
> Internalization of hD1 and hD1-KLH was confirmed by confocal laser scanning microscopy (CLSM). iDCs were incubated with 10 μg/mL hD1, hD1-KLH, AZN-D1, or isotype control 5G1.1 and mouse IgG1 antibodies for one hour at 37°C. Cells were fixed on poly-l-lysine–coated glass slides, followed by intracellular staining with Alexa Fluor 647–labeled secondary antibodies. Cells were imaged with a Bio-Rad MRC 10^{24} confocal system operating on a Nikon Optiphot microscope and a Nikon × 60 planApo 1.4 oil immersion lens (Bio-Rad, Hercules, CA). Pictures were analyzed with

> Bio-Rad Lasersharp 2000 and Adobe Photoshop 7.0 (Adobe Systems, Mountain View, CA) software.
>
> KLH binding and internalization by iDCs was assessed by direct labeling of KLH using the Alexa Fluor 488 labeling kit (Molecular Probes). iDCs were incubated with 10 µg/mL labeled KLH for one hour at either 4°C or 37°C. Subsequently, cells were washed and analyzed by flow cytometry.

275. In the "Results" section, the "Humanized anti-DC-SIGN antibody hD1 is internalized by iDCs" states:

> The CDRs of the mouse antihuman DC-SIGN antibody AZN-D1 were grafted onto a human IgG2/IgG4 composite antibody to generate a humanized antibody for DC-SIGN targeting, hD1. We have previously shown that the human hybrid IgG2/IgG4 constant domain prevents antibodies from binding to Fc receptors.[17] The binding affinity of hD1 for DC-SIGN was similar to that of AZN-D1 as determined by surface plasmon resonance (3.7 ± 0.7 nM and 3.8 ± 1.1 nM, respectively, data not shown).
>
> Flow cytometric analysis revealed specific binding of hD1 to DC-SIGN on iDCs, as preincubation of iDCs with AZN-D1 efficiently reduced binding (Figure 1A). Furthermore, hD1 bound to DC-SIGN–expressing K562 cells after transfection with DC-SIGN cDNA, whereas it did not bind to untransfected K562 cells (data not shown). A time-course internalization experiment revealed that both the hD1 and the AZN-D1 antibodies were rapidly internalized by iDCs, although the AZN-D1 antibody was internalized slightly more efficiently than hD1. As expected, the control AZN-L19 antibody, directed against CD18, was not internalized (Figure 1B). Analysis by confocal microscopy confirmed internalization of the hD1 and AZN-D1 antibodies by iDCs, whereas the control antibodies 5G1.1, directed against human terminal complement protein C5, and mouse IgG1 isotype were not internalized (Figure 1C).

276. Figure 1 shows the binding of hD1 to DC-SIGN and internalization by DCs:

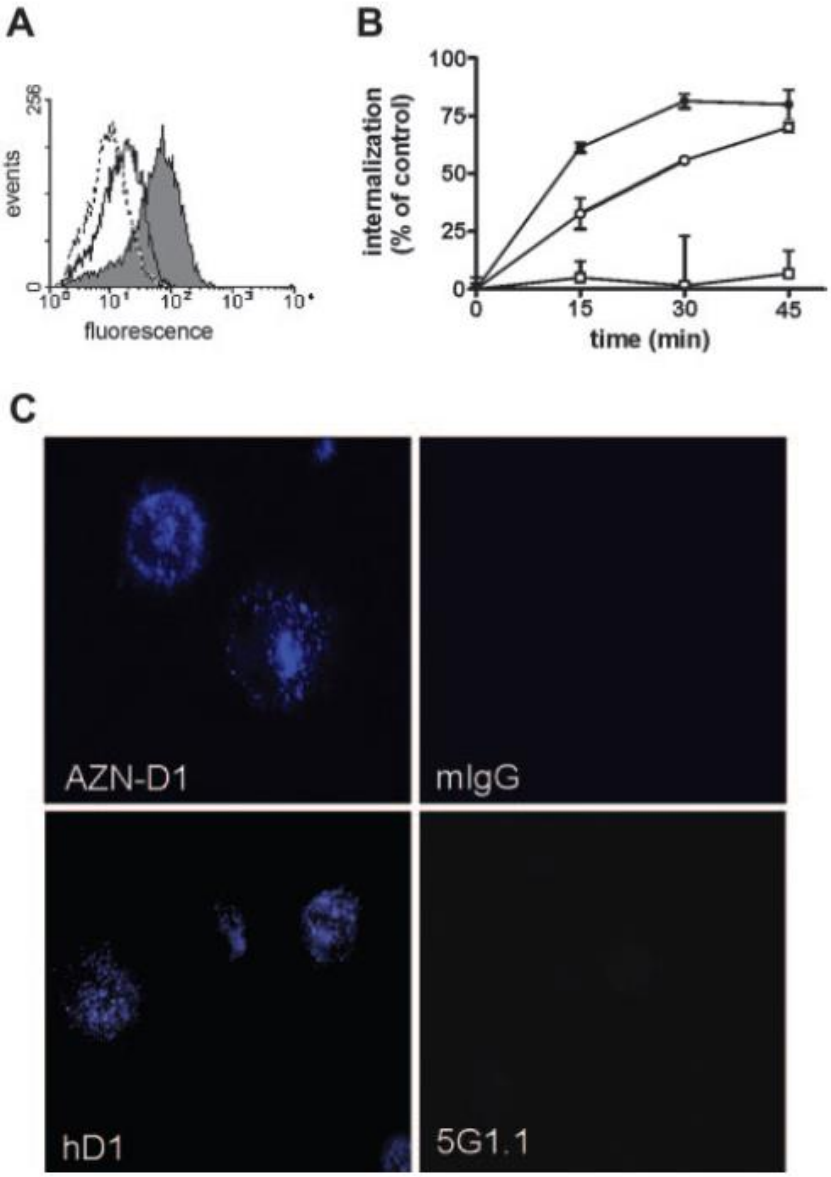


Figure 1. Binding of hD1 to DC-SIGN and internalization by DCs. (A) iDCs were treated with 10 μg/mL hD1 (gray shaded curve), 100 μg/mL AZN-D1 (open dotted curve), or pretreated with 100 μg/mL AZN-D1 followed by 10 μg/mL hD1 incubation (open solid curve), followed by incubation with an Alexa Fluor 647–labeled goat anti–human IgG antibody. Binding of hD1 was analyzed by flow cytometry. (B) iDCs were incubated with AZN-D1 (●), hD1 (○), or AZN-L19 (□) at 4°C for one hour, and transferred to 37°C. Cells were fixed at various time points, and stained with Alexa Fluor–labeled secondary antibodies with or without prior permeabilization. The mean fluorescence was determined by flow cytometric analysis, and the amount of internalized antibody was plotted as a percentage of the amount of total cell-associated antibody. Data represent experiments performed in triplicate ± SD. (C) Internalization of hD1 was confirmed by CSLM. iDCs were incubated with hD1, AZN-D1, or their isotype controls 5G1.1 and mouse IgG1 (mIgG) for one hour at 37°C. Cells were stained with Alexa Fluor 647–labeled secondary antibodies (blue), followed by microscopic analysis. The image represents the middle focal plane of the DCs, with iris set at 2 nm. Original magnification, ×600.

Disclosure of Hillmen 2006

277. Hillmen 2006 is a clinical article in the New England Journal of Medicine. It is not cited art, but it is a specific document that the Defendants allege was CGK.

278. The title is "The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria" by Peter Hillmen and others.

279. Column 1 on page 1234 describes eculizumab as follows (citations to footnote numbering included):

> Eculizumab (Soliris, Alexion Pharmaceuticals) is a humanized monoclonal antibody directed against the terminal complement protein C5.[13] In a preliminary, 12-week, open-label clinical study involving 11 patients with PNH, eculizumab reduced intravascular hemolysis and the patients' transfusion requirements.[14] However, this two-center, uncontrolled study did not have a control group or predefined criteria for the administration of a transfusion, such as a predefined hemoglobin level at which transfusions were administered or a prespecified number of units of packed red cells for a given hemoglobin level.

280. The "References" section lists footnote 13 as follows:

> 13. Thomas TC, Rollins SA, Rother RP, et al. Inhibition of complement activity by humanized anti-C5 antibody and single chain Fv. Mol Immunol 1996;33:1389-401.

Anticipation over Bowdish with Evans

281. There was no dispute about the basic test for anticipation: there must be clear and unmistakable directions. The argument is all about disclosure since there is no dispute that if eculizumab were disclosed, the skilled person could make it.

282. The anticipation case is quite different from the obviousness case over Bowdish with Evans, in particular because it does not depend on motivation.

283. I think it is important to the arguments in this case to appreciate that some prior art just is not entirely clear, and that not all scientific work reported in patent applications is done, or described, perfectly. I say this because I think that in a number of ways the Defendants' case takes as assumptions that *something* is being clearly described in Bowdish (by reference to Evans) and that the work (in particular Example 4 of Bowdish) is done with the correct, optimal controls, and then uses those assumptions as part of working out what the disclosure is. This is not legitimate. A clear example is the Defendants' contention that the 5G1.1 in Figure 14 of Bowdish must be a full length humanised version because otherwise it would not be the optimal control to compare with 5G1.1 + peptide from Figures 13A and 13B. These points have particular resonance given that it is clear that Example 4 and Figure 14 are *not* clear or perfect. The 3º control is unquestionably confusing and Mr Buss accepted that the experiment was "sloppy".

284. I have set out the disclosure of Bowdish and of Evans above. As it explains, the concern of the workers in Bowdish was to graft mimetic peptides into the CDRs of other antibodies for enhanced binding and stability. In Example 4 they were using antibody constructs from Evans. Their concern was not to do with complement mediated disease, but that would not matter for anticipation, if something within claims 1 and 2 were disclosed sufficiently clearly and unambiguously.

285. The Defendants' anticipation case is that as per [0191] Bowdish started with an antibody called 5G1.1, and then replaced its CDR-H3 to give what is shown in Figures 13A and 13B and which is called "The 5G.1+peptide", "produced as a whole antibody". That does not anticipate because it has the mimetic peptide sequence, but the Defendants say that the antibody pre-replacement does anticipate. Its sequence is not explicitly stated but the Defendants say that it is clear what it would be.

286. "Additionally or alternatively" the Defendants say that the "parental 5G1.1" referred to in [0192] in connection with Figure 14 is an anticipation. This depends on its (a) having the pre-replacement CDRs from Evans, (b) being human not (as Alexion contends is at least possible) murine and (c) being a full length IgG2/IgG4 isotype antibody (Alexion says it might be a fragment).

287. In their closing submissions, written and oral, the Defendants objected to Alexion running the argument that the reference to parental 5G1.1 in [0192] might be to a fragment. They said that that possibility was nowhere to be found in Prof Nimmerjahn's reports or in Alexion's written opening submissions and that accordingly they had not cross-examined to it, it having raised its head for the first time in Mr Buss' cross-examination.

288. Although the basis for the argument in Prof Nimmerjahn's report and in Alexion's written opening was slight I do not think it was wholly absent. Both contained references to the range of antibodies and antibody fragments in Evans and [0191] says that 5G1.1 comes from Evans.

289. Evans is also where I think the real novelty analysis starts. Bowdish [0191] begins by saying that the TPO mimetic graft has been transplanted into another antibody framework, 5G1.1, whose construction is to be found in Evans. On its own that tells the skilled person to look to Evans. Two things are said to have been done: the mimetic sequence is cloned in to whatever 5G1.1 is, and the resulting 5G1+peptide "was produced as a whole IgG antibody", with sequence given in Figures 13A and 13B.

290. Figures 13A and 13B are human sequences, and 13A is an IgG2/IgG4 hybrids. They are not explicitly stated to be human but the skilled person could work that out easily.

291. In [0192] the skilled person then learns that "Purified 5G1.1+peptide antibody" as well as "the parental 5G1.1" were analysed for their ability to bind; and other negative and positive controls were used as well. Binding was tested to cells with the receptor relevant to the mimetic, and to cells without the receptor. The overall

objective was to show that the antibody with the mimetic bound to the receptor by specific recognition.

292. I agree that there is clarity about what the 5G1.1+peptide was, since its actual sequences are given in Figures 13A and 13B. It is not spelled out by what process it was arrived at, but [0191] reads as if the CDR replacement was done and then production as a whole IgG antibody was done, in which case there would be not be any intermediate corresponding exactly to eculizumab, certainly not disclosed sufficiently unambiguously, and I understood the Defendants really to focus on "the parental 5G1.1" in [0192].

293. To my mind, "parental 5G1.1" is not unambiguous. "Parental" is sometimes used in this field to refer to the original murine form of an antibody, as the Defendants accepted (and the cognate noun "parent" is used that way in Evans, in fact, at column 50), but it is not a term of art with a clear and unvarying meaning. I can accept that it might be used in a more general way to connote a prior form or something from which the current form has been derived, and it is possible that context could make that clear, but I do not think the context in [0192] does so.

294. Additionally, if "parental" was used in this more general sense, what is being described is still "parental *5G1.1*" and the skilled person has been told in the previous paragraph that 5G1.1 is described in Evans. So the reader would think it was at least possible that a reference back to something actually in Evans (specifically Example 11, Alexion said) was being made, and it was in support of that thinking that Alexion raised the possibility of a fragment being used. Alexion also maintained the possibility that the full length murine antibody from Evans was being used.

295. At this level, I think Bowdish is just not clear about what was done. But in an effort to bring clarity, the Defendants relied on the following points:

    i) Figures 13A and 13B can readily be seen to be human.

    ii) Since, therefore, 5G1+peptide is human, the parental 5G1.1 must be human since it would make no sense to use a murine control as a comparator.

    iii) It is additionally clear that the parental 5G1.1 must be human because it was detected by (polyclonal) goat anti-human IgG.

    iv) It would also not make sense to use a fragment parental 5G1.1 because the difference in Fc between it and the full length 5G1.1+peptide would prevent certainty that any difference in binding was purely due to the mimetic substitution.

296. As to the point about Figures 13A and 13B being human, I do not think that is clearly and unambiguously disclosed. It could be worked out fairly easily but I think that is a process of inference and not something actually disclosed by Bowdish. I acknowledge that this is a close call and there could be sequences which the skilled person could at a glance identify as human (or not, as the case may be). So I will proceed from here on the basis that I might be wrong about

that and that there is sufficiently clear and unambiguous disclosure that 13A and 13B are human.

297. Assuming that the skilled person did clearly and unambiguously think that Figures 13A and 13B were human, it would seem unlikely that a murine "parental" was used as a control in Figure 14 if the experiment was done sensibly. This is both because of the undesirability of having a control which differed not only in not having the mimetic but also in the species from which it was derived, and also because of the point about the goat anti-human IgG. Prof Nimmerjahn said that it was possible that polyclonal antibodies could bind to murine antibodies but it was a tenuous suggestion and the choice would still be an odd one. Prof Nimmerjahn's evidence on this particular point was also somewhat affected by his not initially having taken on board that Figures 13A and 13B were human.

298. The idea that the parental 5G1.1 might be a fragment, especially a human fragment, would make more sense. It would make textual sense because of the way 5G1.1 is said to have come from Evans, to which I have already referred, and although it would mean that the control was not perfect (because it would not provide an isotype control), on the evidence I find that it would still provide useful information because it would have the original CDRs and would allow it to be demonstrated that the CDRs themselves were not responsible for binding to the receptor. And indeed Mr Buss accepted that Fabs and full length antibodies are compared in the same experiment in Bowdish in respect of the Fabs from Example 1, although he disagreed about the implications.

299. I also note, although it is a relatively minor textual point, that the 5G1.1+peptide is occasionally referred to in [0192] and [0193] explicitly as a whole IgG antibody but the parental 5G1.1 never is. Finally, it was effectively common ground, and I would anyway find, that the 3^{o} control was unclearly described. This does not go directly to the Defendants' chain of logic but it is part of the picture of confusion and lack of clarity.

300. For these reasons I conclude there is not a sufficiently clear and unambiguous disclosure for anticipation. The Defendants' arguments are in truth much more along the lines of what control it would be obvious to use for the experiment in Figure 14 if the best comparison was to be made and the skilled person had a free hand; that is not the right approach for anticipation. Some of the points made by Alexion and/or Prof Nimmerjahn were rather tenuous, but that can happen when one is seeking to explain something that is not clear, and Alexion's task was merely to show that other readings were possible. I actually think Alexion's case is more faithful to the text of [0191] and [0192] than the Defendants', because of the reference to "5G1.1".

Anticipation of claim 2

301. Since claim 1 is not anticipated, claim 2 cannot be either. But in case I am wrong about claim 1 I will deal with claim 2 on the basis that claim 1 is anticipated.

302. I have dealt with the meaning of claim 2 above. It does not require intention, merely that the product comprising the antibody would be suitable for use as a pharmaceutical composition.

303. It is not possible to tell from Bowdish what the specific form of parental 5G1.1 was. This is not a promising start for clear and unambiguous disclosure, although I accept that as a general matter it can be inferred with confidence that it was in a presentation suitable for the experiment of Figure 14, which would require it to be in solution.

304. Mr Buss did not say in what form it was. He was not cross-examined on the topic but since he had said nothing about it I do not think there was any obligation to challenge him.

305. Prof Nimmerjahn was asked some questions but they were very general and did little more than establish that the antibody was very likely to be in a buffer. That is not inconsistent with its being in a pharmaceutical composition but does not show that it was.

306. Counsel for Alexion said in argument that it could not be excluded that the antibody might aggregate in such a way as to be unsuitable as a pharmaceutical, or might be with a toxic ingredient. There was no specific evidence to support these possibilities but at a conceptual level they illustrate why the mere fact of being in solution is not enough.

307. This is all too vague and general and I reject the anticipation case against claim 2, even if claim 1 were anticipated.

Obviousness – the law

308. There was no disagreement about the basic approach, which may be found in the decision of the Supreme Court in *Actavis v. ICOS* [2019] UKSC 15 at [52] – [73]. I also bear in mind the statement of Kitchin J, as he then was, in *Generics v. Lundbeck* [2007] EWHC 1040 (Pat) at [72], approved in *Actavis v ICOS*.

309. Obviousness is often argued by parties, and decided by judges, using the structured analysis in *Pozzoli v. BDMO* [2007] EWCA Civ 58. It is not mandatory, however, and was not used by the parties at trial in developing their primary arguments. I address this next and conclude that it was not a problem in the circumstances of this case

Obviousness over Bowdish with Evans

310. Neither side really analysed this issue in a *Pozzoli* fashion. The Defendants provided a brief couple of paragraphs on a *Pozzoli* basis in their closing written submissions but it was not much more than a conclusion.

311. I do not think it is compulsory in all cases to use a *Pozzoli* analysis and the unusual nature of the obviousness arguments in this case make it a difficult fit. I would have been more troubled if either side had said that *Pozzoli* gave a different result, but neither did.

312. In any event, I have dealt with what would be the initial steps in *Pozzoli*, above, identifying the skilled team and the CGK. I have said that the skilled team would include a clinician and that the CGK would include knowledge of eculizumab as a successful treatment for PNH. I also observed that even if the skilled person would be only an antibody engineer as envisaged by Alexion, that person's CGK would include eculizumab as a treatment for PNH.

313. Those conclusions as to the skilled person and CGK form the platform for the obviousness argument over Bowdish.

314. The Defendants' main argument seemed to me to be as follows:

    i) The skilled team, at the instance of the clinician, is interested in replicating or improving eculizumab.

    ii) Hillmen 2006 was CGK.

    iii) To work on eculizumab the skilled person would be interested in finding out its clone name.

    iv) They could find that out from Thomas, which would be identified by routine means from Hillmen 2006, although it (Thomas) was not CGK in itself.

    v) Then when presented with Bowdish the skilled person would see 5G1.1 and associate it with eculizumab because they would know the clone name from Thomas.

    vi) The skilled person would see that 5G1.1 was what was in Figures 13A and 13B but with the CDR-H3 from Evans put back in.

    vii) The skilled person would appreciate that it was likely that between Thomas and Bowdish there had been further development of the antibody. They would see but not be surprised by the change at position L38 to the germline glutamine.

    viii) They would also see that figures 13A and 13B had an IgG2/IgG4 hybrid constant region. Since that was not necessary or relevant to Bowdish's experimental purpose, the skilled person would assume that it was something that had been done for clinical development reasons.

    ix) The skilled person would think that figures 13A and 13B with the CDR-H3 changed back would actually be eculizumab, but even if they did not they would think it obvious to make and test it.

315. Alternatively to the above, the Defendants said that the skilled team would get the clone name from a PubMed search. That such a search could be done and what it might show was supported by some of Mr Buss' written evidence but the alternative argument was very much a second string and a defensive resource for the Defendants against problems associated with relying specifically on Thomas.

316. I could accept an obviousness case might legitimately start with steps i) to iv) above, each of which I individually accept. But that sets the skilled person on a

course towards a specific goal in which they are guided by Thomas, which is not a CGK document. The course of the obviousness case does not then follow on from Thomas, however, because the skilled person could not use the clone name they had acquired to get the sequence of eculizumab (they might try CAS, one could suppose, but that would be a dead end). Instead, the obviousness argument jumps abruptly across to Bowdish and inserts it, with Evans, at just the point where the skilled person has (analytically speaking) picked up the clone name, sequences and so on from Thomas.

317. It is of course legitimate for a party attacking a patent for obviousness to choose its prior art, and to have it appropriately assessed in the light of the CGK even if it is obscure or from a different field. But that does not entitle such a party to mosaic its prior art with another non-CGK document just because that other document is one that would be found from a CGK source given a specified goal to start from. Even if particular circumstances might justify it in some cases, it carries with it a severe risk of hindsight, and the Defendants' case at this early stage in its analysis is very much hindsight: defining a project, getting to Thomas, then pausing and plugging in Bowdish and Evans at just the right point.

318. So I conclude that the Defendants' obviousness case over Bowdish fails at the outset because of being an illegitimate mosaic with Thomas.

319. Even were that not so, I would reject the attack because the remaining steps listed above, even if individually sound, are an illegitimate *Technograph* ([1972] RPC 346) stepwise exercise.

320. I do not in any case think that the individual steps are sound. Some are quite speculative. In particular, the steps associated with the assumption that Bowdish concerns something that is the result of clinically-driven development are very uncertain. Bowdish is an experimental paper and when it was actually done relative to Thomas and Hillmen 2006 (which came later) is unclear. There is also of course the general lack of clarity about the "5G1.1" constructs used in Bowdish, which I have discussed in dealing with the anticipation attack.

321. It is also fatal to the attack that the way Mr Buss identified during cross-examination for the skilled person to know or think that Figures 13A and 13B related to eculizumab was to build in knowledge from Tacken/Mueller that eculizumab had a hybrid backbone.

322. As to the argument that the skilled person would take Bowdish's Figure 13A and 13B with the restored CDR-H3 into the clinic even without knowing that it was eculizumab, I reject it for three reasons. First, it comes, analytically speaking, at the end of a long line of suppositions, second it does not match the initial task set by the Defendants for this attack of replicating or improving eculizumab, and third because although Prof Nimmerjahn said that the IgG2/IgG4 hybrid could be used to treat patients in addition to using an IgG4-only backbone, this was no more than accepting a possibility. He did not accept obviousness, or that there was any particular expectation of a good or better result or that the skilled person would understand what was going on.

323. I also reject the Defendants' alternative argument that the clone name might come from a PubMed search. The Defendants' real case was firmly based on Thomas and I would not accept an argument that the skilled person would look at Hillmen 2006, *not* check Thomas and then get the clone name from PubMed instead. Even if the attack could leave Thomas out of account that would leave the skilled person reading Bowdish with just the clone name and no detailed information about what eculizumab was. The skilled person would probably be more likely to think that Figures 13A and 13B were experimental constructs, lacking the basis from the Defendants' main argument to think about the development flow from Thomas to Hillmen 2006.

Obviousness over Tacken with Mueller and Thomas

324. The Defendants' case for obviousness over Tacken is as follows. As I narrate it, I will identify the key points of agreement and dispute.

325. First, the Defendants accepted that Tacken is not concerned with anti-C5 antibodies, or at least not directly, and nor is it about complement therapy. It is about a different scientific interest, namely targeting human dendritic cells with a humanised anti-DC-SIGN antibody (called hD1V1G2/G4).

326. However, the Defendants relied on the principle that the skilled person is deemed to read the prior art with care (albeit that they do so without any particular expectation that it will contain anything useful, let alone a solution to any particular problem). As a result of this careful approach, the skilled person would read the disclosure about recombinant antibodies on page 1279 and also read the description of the experimental methods. I understood that at a general level Alexion accepted this, but anyway I agree with it. However, Alexion made clear that because of the principle that the skilled person does not have a preconception that a document will contain anything useful, an undue focus on the sentence about eculizumab would be a wrong approach. I agree with this reservation, too.

327. Second, the Defendants said that the skilled person would be motivated to make eculizumab using the disclosure, and that that disclosure essentially tells the skilled person that eculizumab has the hybrid constant region of Mueller and the humanised variable region from Thomas.

328. In relation to disclosure of the "Recombinant antibodies" paragraph, the Defendants said that it was simple and clear on its face. They relied in particular on the fact that in the experimental work of e.g. Figure 1C, that which is denoted "5G1.1" unambiguously has an IgG2/IgG4 hybrid constant region.

329. Alexion did not accept any of this, and argued that the disclosure is unclear and indeed says or tends to suggest that the hybrid backbone was only for experimental purposes in Tacken, not for eculizumab, and that the reader would think that eculizumab still had an IgG4 backbone (as in Thomas, and as was generally more common).

330. Alexion also argued that the skilled person who was trying exactly to replicate eculizumab would have no way of knowing whether or not they had succeeded, whether by obvious means or not.

331. Third, the Defendants accept that the combination of the Mueller constant region and the Thomas variable regions does not meet the requirements of the claims of the Patent on Alexion's construction, because at residue 38 of the light chain Thomas has arginine (R) while SEQ ID NO: 4 in the Patent requires glutamine (Q), but they say it would be obvious to make this change, or alternatively to try both.

332. On this third aspect, Alexion argued that it was not obvious which amino acid ought to be used at position 38 if the skilled person was determined precisely to replicate eculizumab and that the route to choosing the glutamine at position 38 was (a) dependent on the non-CGK Martin abYsis sequences, and (b) tainted by hindsight, in particular as revealed by the cross-examination of Mr Buss who referred to Evans in the course of his answers on Tacken.

333. Alexion also argued that it was necessary to the Defendants' case that the skilled person would not change any *other* residues.

334. I note in passing that there was a point of detail about adding an "A" residue prior to adding the Mueller sequence, but it was common ground that this would be done without invention if the assembly of components argued for by the Defendants was otherwise to be undertaken. It was not said by Alexion to add anything.

Degree of interest?

335. As I have already said, the skilled person is not deemed to read Tacken with any expectation that it will be of interest, or useful. They certainly do not expect in advance that it will explain how to make eculizumab. Nonetheless, the law requires that they read it with care and that means that they will at least see that something called eculizumab is described in the key paragraph, in a publication from Alexion themselves, with references. Since their CGK would include that eculizumab was a successful treatment for PNH, they would be interested in at least understanding what was said. It would be apparent without any invention at all that if the characteristics of eculizumab were indeed described it would be desirable to make and/or optimise it. Both as a matter of law and as a matter of reality on the evidence the skilled person would seek to understand the paragraph in the context of the rest of the document.

336. I also find that this would necessarily mean that they would want to follow up and read Mueller and Thomas.

What does the paragraph mean?

337. The absolutely central text is the last sentence of the paragraph, "An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [sic], Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[19]". Reference 19 is Thomas.

338. The sentence needs to be read in the context of the paragraph as a whole; for example the reference to "the same" is a reference back.

339. Although "eculizamab" is an error, I do not think anything turns on it. It is just a typo. It was faintly suggested by Counsel for Alexion in cross-examination that it would undermine the reader's confidence generally, but I reject that.

340. Alexion said that the natural meaning of the sentence is that eculizumab has the sequence in Thomas and that the hybrid was something added only for Tacken's experiment. It pointed out that Thomas does not mention a hybrid constant region, that the reader would see that in Mueller the hybrid was also just for experimental reasons, that there would be no reason apparent in or from Thomas for changing from the IgG4 constant region, and that the reference to Thomas would serve no purpose if eculizumab was not disclosed in it. It also pointed out that Hillmen 2006, in referring to Thomas, did not mention a hybrid backbone.

341. Alexion also said (seeking to rebut a suggestion in the Defendants' written openings) that if Tacken was unclear, that was not good enough for the Defendants, especially in the context of a skilled person charged with precisely replicating eculizumab.

342. I think the paragraph and the key sentence are really very clear, and certainly when it comes to the question of the hybrid backbone. Tacken is very clear when setting out the work in Figure 1 that it is calling an antibody with a hybrid backbone "5G1.1"; it expressly also refers to this as "eculizamab", in terms, and associates that with "the same IgG2/IgG4 constant region". This all makes sense with the use of 5G1.1 as an isotype control antibody.

343. I therefore conclude that the Defendants are right about the disclosure of Tacken as a matter of pure construction. As to Alexion's points:

    i) I agree that the hybrid set-ups were used as controls, both in Tacken and in Mueller. But that is not inconsistent with eculizumab having a hybrid backbone; that may just have made it a convenient control that was to hand at Alexion.

    ii) I agree that Thomas does not mention a hybrid constant region. But I accept Mr Buss' evidence that the skilled person would know that Thomas was a paper written at a relatively early stage of development and that subsequent development and optimisation was likely to have happened. That does not mean that the skilled person would think it definitely had happened, but they would not view a difference between the earlier Thomas description and the later Tacken one with any alarm.

    iii) The skilled person would think that Thomas was being referred to in connection with the variable binding regions; that makes sense in terms of where the reference is given, at the end of the paragraph. The reference would therefore not be pointless. The binding regions were not, it is true, relevant to what Tacken was using 5G1.1. for, so the reference to Thomas is informative and not critical. But it would perhaps allow the Tacken work to be reproduced if desired.

    iv) I do not think the Hillmen point adds anything to the fact that Thomas does not mention a hybrid framework.

344. In connection with the possibility that the sentence is ambiguous, I simply do not think it is in relation to the hybrid backbone issue. Alexion's point about the skilled person never having certainty that what they made was eculizumab does not work at that level; the skilled person would be very confident that they were being told eculizumab had a hybrid backbone and they would not be troubled by Thomas not having mentioned it, for reasons I have already addressed.

345. However, the lack of certainty for the skilled person does have a potential part to play in relation to residue 38, for reasons I will now come to as I address that topic.

The arginine at position 38

346. The Defendants' case is that the skilled person who had read and concluded that eculizumab consisted of the constant regions from Mueller and the variable regions from Thomas, would then check the sequence before considering making or testing it. I have no doubt that that is correct. I also accept, consistently with what I have said above, that their consideration would be informed by the fact that Thomas was an early paper, after humanisation but before any optimisation.

347. The Defendants then say that position 38 in the Thomas sequence would stand out as one where Thomas had kept the murine residue. This would present the risk of additional immunogenicity without, probably, any benefit in terms of binding.

348. The Defendants fortified their position by:

    i) Pointing out that Thomas specifically identifies position 38 (left hand column on page 1394).

    ii) Reliance on the CGK about this kind of optimisation. I have dealt with this above.

349. Alexion on the other hand said that:

    i) The skilled person would only think about making a change if a problem arose.

    ii) Mr Buss had mosaicked in Evans which undermined his logic and his credibility.

    iii) Mr Buss had relied on modern tools (abYsis) and did not know what result they would have produced in 2007.

    iv) Because of the uncertainty about abYsis it could not be said what other changes might have been thought obvious in 2007 and any other change would have taken the result outside the claims.

    v) The skilled person would never know if they had in fact replicated eculizumab because they would not have a definitive sequence to compare against.

350. I will address the point about Mr Buss mosaicking first. I agree that in the course of his cross-examination he did refer to Evans on the point about position 38. It was somewhat confused but it was clear that in that part of his evidence he was combining in Evans on position 38. Possibly part of the problem was that the Defendants had at various times and in various ways relied on real-world events as secondary evidence that their approach to position 38 was reasonable and had in fact been adopted by skilled people. Whatever the reason, Mr Buss did rely on the mosaic with Evans to an extent.

351. However, I do not think that some illegitimate reliance on other prior art at some point in an expert's evidence necessarily justifies entirely rejecting their evidence or the position that it supports. It depends on the nature and degree of reliance and whether it infects other things that they say.

352. In the present case and in relation to Tacken/Evans I think Mr Buss' essential views on obviousness over Tacken were reached and expressed without reliance on Evans. For reasons I have dealt with above and am coming to in more detail they had a solid foundation in the permissible prior art and the CGK. It is I think especially clear that there is nothing artificial or synthetic in identifying position 38 as important and it does not need hindsight or other prior art to do so. The whole point about position 38 is that it is a murine residue in Thomas at a position that one would like, based on the CGK, usually to be human for immunogenicity reasons if binding did not have to be sacrificed, so it is not as if Evans was necessary to provide the idea of making the residue the same as in the germline.

353. I have also considered carefully how I ought to regard Mr Buss' reliance on Evans in the context of Tacken given that he illegitimately relied on Tacken when defending his views on obviousness over Bowdish with Evans. I have to consider, and do, whether this amounts to a pattern reflecting on Mr Buss' evidence across the board. However, I think the two incidents were actually very different despite their superficial similarity. In relation to Bowdish and Evans there was simply no legitimate way to know that eculizumab actually had a hybrid backbone so adding in Tacken was a fundamental point. By contrast, as I have said, there was plenty of legitimate material, in Thomas and in the CGK, to point to position 38 meriting the skilled person's consideration in relation to the obviousness case over Tacken.

354. With these matters in mind I do not think the inclusion of Evans during Mr Buss' oral evidence on Tacken materially undermines the force of his evidence on the topic. Of course, I cannot factor in Evans on the point.

355. I return to Alexion's other points.

356. As to the argument over whether the skilled person would make a change before there was an actual problem, I prefer Mr Buss' evidence as more practical and realistic and I have very largely already addressed this in connection with the CGK. The skilled person would be able to see that there was a real risk of unnecessary additional immunogenicity in keeping the murine residue and would routinely seek to iron it out as part of the optimisation process. As a practical matter, all this would involve would be making two versions of the antibody, with both possibilities at position 38. The skilled person would have a high degree of

confidence that the version with the human residue at position 38 would not compromise binding but would be able to find out by a simple binding experiment. If binding was maintained then the human residue would be preferred as less likely to cause immunogenicity and further tests on that attribute, or waiting to see if there was a problem further down the road, would be avoided.

357. As to the abYsis point, I consider that was a red herring. The Defendants did not positively rely on abYsis as to how the skilled person would reason at the priority date. Their case was based in this respect on CGK (both as to the general approach and as to position 38 specifically) from McCafferty. abYsis only came up because Mr Buss used a modern version of it to seek to show that glutamine is in fact far more common at position 38 than arginine and that the latter is very uncommon (1% frequency). Mr Buss specifically said that abYsis was not available at the date but that it showed the sort of thing the skilled person would have found. The sort of thing the skilled person would have found is evident at the necessary level of generality from McCafferty and that is why abYsis is a red herring.

358. As to the possibility of other changes, Alexion relied on abYsis for this, mainly, arguing that without contemporaneous evidence of what abYsis would have shown the Defendants could not demonstrate that there would no other changes to consider if the skilled person were pursuing the approach for which they were arguing. I reject it for the same reason: abYsis just does not enter the picture. In any event, had there been any mileage in the point that other changes might have occurred to the skilled person there would have been nothing to prevent Alexion from pointing to other changes that could or would have entered the picture at least for consideration, and it did in fact try to show that in the cross-examination of Mr Buss, but the questions failed on the facts and were withdrawn after the Defendants pointed out the error underlying them.

359. The last point I come to is the one about whether the skilled person would ever have known that they had in fact precisely replicated eculizumab, on the assumption that that was the task they had set themselves, or that the skilled clinician had given the skilled antibody engineer.

360. I agree that in relation to position 38 the skilled person would not and could not have certainty that they were precisely replicating eculizumab (matters are different in relation to the hybrid backbone where I think the skilled person would have very high confidence about what Tacken was saying). There are however two related answers to this point:

    i) First, I do not think it is fair to say that the Defendants' case was limited to precisely and completely replicating eculizumab at all costs or else giving up. The Defendants' experts' evidence was on the basis of replicating *or optimising* eculizumab.

    ii) Second, the skilled person's approach would be a practical one and ways forward could easily be tested: see above.

361. As a result, I think the skilled person would approach the position 38 issue with the attitude that they were very confident that an antibody with the human residue

at position 38 either was exactly eculizumab as used in the clinic, or would be an optimised version of what was used in the clinic (with the same binding and at least potentially lower immunogenicity risk). It would be obvious to make and test both, and the expectation would be that the version with the human residue at position 38 would be as good as or better than the (Thomas) version with a murine residue there.

362. For all these reasons I conclude claim 1 is obvious over Tacken with its cross-reference to Mueller and Thomas.

363. I have used a lot of words to reach this conclusion; probably too many. In my defence, a lot of points were taken, and I also had to deal with the mosaicking point about Mr Buss. When a lot of points are taken on an obviousness attack, and the nature of writing a judgment is that they have to be dealt with in sequence, the impression can arise that the attack is too *Technograph*, too hindsight salami-slicing. I have therefore given specific consideration to that risk and in particular in the light of Mr Buss' mistaken reliance on Evans during his oral evidence.

364. In my view, the attack is actually a simple one, and I do not mean simple in hindsight. The skilled person is interested in eculizumab for important clinical purposes, and they are given a document from the antibody's originator, albeit written for a different purpose, which appears to describe its necessary component parts in fairly clear and simple terms by referring to two other papers from the same stable. They think about how best to replicate it and have a high degree of confidence in being able to make and test something identical or if not identical then at least as good or better. Nearly all the points I have had to address above are matters where Alexion tried to put obstacles or confusion in the way of this and which I have rejected. They are not additional obstacles or decisions as one gets with a hindsight stepwise attack.

Claim 2

365. Alexion reserved its position on claim 2 over Tacken in case the Defendants made some sort of case that was not dependent on clinical desire to use the antibody. This did not come to pass and Alexion rightly accepted that claim 2 is not independently inventive over claim 1 in the face of the argument that the Defendants made.

INSUFFICIENCY, LACK OF TECHNICAL CONTRIBUTION, AGREVO OBVIOUSNESS

366. I have concluded that the Defendants are right about claim construction, on which basis Alexion accepts that the Patent should be revoked, and that the Patent is obvious over Tacken in combination with Thomas and Mueller.

367. The Defendants also argued that the Patent was invalid under one or more of these other legal heads, all for very similar and overlapping reasons based on the fact that the Patent says that eculizumab was not new, and does not assert a technical contribution arising from identifying eculizumab's sequence for the first time. A

subsidiary point was that the Patent does not identify any specific advantage in the change at position 38 with respect to Thomas.

368. I think the Defendants failed to think through that these arguments would only matter in the event that they were wrong on claim construction. In that case, it would follow that the skilled person would think that eculizumab was not accepted by the patentee to be old, that the reference to Evans disclosing it was incorrect, that the inclusion of the leader sequence in SEQ ID NO: 4 was to be ignored as not being sensible, and that what the patentee really meant was eculizumab.

369. In that scenario the skilled person would think that they were being told something new and potentially inventive by the Patent, namely the sequence of eculizumab, and indeed (again, only in this scenario where the Defendants had lost on the upstream issues) they would be right. It would not be spelled out in the Patent in quite the way that Alexion now puts it, but it is well-established that a patentee can recharacterize its technical contribution in the face of prior art attacks. Patentees cannot be expected to anticipate how they would put their contribution in relation to all prior art. Essentially the same goes for the fact that position 38 is not called out as being different from Thomas.

370. I therefore conclude that these attacks are not needed in the event that I am right about claim construction and obviousness and do not work if I am wrong.

THE UPC DECISIONS

371. Alexion requested that the application for the Patent should proceed as a Patent with Unitary Effect following grant, and has brought proceedings in the UPC against Amgen and Samsung Bioepis, based, for reasons that have not been explained to me, only on claim 2.

372. Alexion sought a preliminary injunction and at first instance the UPC Hamburg Local Division refused the injunction. It reasoned that Alexion had an argument for infringement on its claim construction but that the literal subject of the claim with the 22 amino acid leader sequence was non-functional because it would not bind C5.

373. The case went on appeal and the UPC Appeal Court ("UPCAC") noted that in the TBA before grant Alexion had said that the antibody with the 22 amino acid leader sequence might bind, but said that the position had changed in the light of Alexion's arguments before it (that the antibody with the 22 amino acid leader sequence was *not* functional). So it agreed with the Local Division that there was a substantial probability of revocation on opposition.

374. However, the UPCAC disagreed with the Local Division on claim interpretation. Relying heavily on the fact that the specification presents eculizumab as old, it held that the claims were limited to the antibody with the 22 amino acid leader sequence. On that basis the claims were invalid for insufficiency on the basis of Alexion's arguments.

375. The UPCAC is consistent with my decision on claim construction. That fortifies me in my conclusion but is not necessary to it. The UPCAC found the claim insufficient as well, because Alexion had positively argued there would be no binding with the 22 amino acid leader sequence present. That is different to the situation I am presented with, but only because the UPC proceeded on the basis of Alexion's own arguments whereas I have evidence that the skilled person would think that there might be binding.

376. The UPC proceedings also further illustrate Alexion's ever-changing positions, but that is not material to my decision-making.

THE NON-TECHNICAL ISSUES

377. I have concluded that Alexion is wrong about claim construction, on which basis there is no infringement and revocation is conceded, and that the Patent would be obvious even if Alexion were right about claim construction.

378. As a result, any decision I made on abuse of process, judicial estoppel or approbation and reprobation would not affect the overall result. It is therefore unnecessary for me to decide them, but I consider that I still should turn my mind to whether it would be desirable for me to do so.

379. None of these arguments raises any disputed question of fact. If there were any disputed questions of fact then I would at least decide them to guard against the possibility that my decision on the substantive patent matters might be overturned on appeal, but that is not the case since all the facts appear from documents which are not challenged. I have identified the high water mark of the Defendants' factual case on these issues in the Introduction to this judgment.

380. By contrast, all of the arguments raise difficult and, Counsel for the Defendants accepted, novel points of law. The estoppel and approbation/reprobation arguments in particular would have the effect of leading to revocation of a patent which (on the hypothesis that they affected the overall result) was both valid and infringed. The abuse of process arguments are in a general sense less controversial but on the other hand I find it hard to see how they could succeed if the other non-technical arguments did not, since they would then fall to be decided on the basis that Alexion was able to argue that eculizumab was not part of the state of the art, and it would merely be contending that a statement made in the specification was incorrect, which happens quite often and which it seems hard to say is positively abusive.

381. To some extent during the trial and increasingly in the preparation of this judgment, I felt and have continued to feel uneasy about whether the legal points were fully and sufficiently argued. I will explain why in a moment. But in view of these concerns I do not think it would be the best course to make a decision on the points. Any decision would necessarily be incompletely reasoned, and to create a new judge-made route to revocation of otherwise valid patents, even if it were plain on its face that it was open to revision in a future dispute with more argument, would be a major step that I do not think should be taken if not necessary.

382. I have also considered whether I should call for further argument in the light of my concerns on the law, but have concluded that to do so would, on balance, not be desirable because it would delay the giving of my judgment (possibly for quite some time) when the overall result is not in doubt.

383. My concerns about the matters not (fully) argued include the following:

i) It was my recollection that there is English case law that a patentee is not precluded from arguing that a statement in the specification of the patent in suit about the prior art/CGK is wrong, although it may be a powerful piece of evidence against them. I asked about this in opening and the parties directed me to *Gerber v Lectra* [1995] FSR 491 (CA), but did not really argue out its reasoning or implications. The judgment is in line with my overall recollection but suggests that there could be no estoppel in the absence of reliance, and goes on to say that a patentee might, or ought, not to be able to resile from a clear and unambiguous statement in the specification if it had led to the grant of the patent or gave the public the impression that validity could not be successfully challenged. See page 495. While briefly expressed, I think the views of the Court of Appeal ought to have been debated in argument at this trial.

ii) Relatedly, I would have benefited from more argument about whether and if so when an estoppel can arise from a statement on which there was no reliance and/or which was made in litigation to which the party raising the estoppel was a stranger.

iii) The judicial estoppel and approbation/reprobation arguments rely on statements made in other litigation and/or in the course of the prosecution of other patents (and not just patents in the same family). English law having taken a sceptical and limiting approach, in the context of reliance on the prosecution history of the actual patent in suit in *Actavis v Lilly*, I think careful analysis is needed of the practical effects of creating the new approach argued for bySB.

iv) The effect of the judicial estoppel and approbation/reprobation arguments would be to make something (the sequence of eculizumab) prior art that in fact is known not to be such. The EPC and the Patents Act 1977 are both very explicit and very limiting about what is prior art and what grounds for revocation exist. See e.g. section 72(1) of the Act which says that patents can be revoked "on (but only on) any of the following grounds …". I raised this with SB prior to the closing arguments and the response, in written closing, was that it was only relying on a permitted ground of invalidity (lack of novelty) and that it was merely a rule of evidence, a matter for national procedural law, which would have the effect of preventing Alexion from saying that e.g. the CAS sequence was incorrect. I understand the contention as a general matter but it is not simple and merits full argument, which did not happen. I would also note that whether or not this is characterised as a matter of procedure it has the capacity to lead to lack of harmonisation with other EPC member states. The complexity is exacerbated by the fact (which Counsel for SB accepted) that there would seem to be no reason why the principle should apply in only one direction

and so there could be a case where a patent which was clearly invalid was saved by some prior art being ruled out on the basis of a previous statement or argument by the party attacking it.

v) In closing arguments, Counsel for Alexion relied on the point that EPO decisions do not create estoppels that are binding in later national litigation on the validity of the same patent (*Buehler v Chronos Richardson* [1998] RPC 609 (CA)) and that that is because they are not final, given the scheme of the EPC and the allocation of roles to the EPO and to national courts under it. It would therefore, it was argued, be illogical if statements made in the course of opposition proceedings did create estoppels. Again, this needed more argument than was realistic given that it came up on the last day of the trial in oral submissions.

384. I do not think these concerns are adequately met by the point that the arguments in this case arise only in the context of very unusual facts. Experience shows that reliance on the prosecution history is attempted reasonably often, and considerably more often than it succeeds. Yet the work of analysis of the file and arguing it still has to take place even when it turns out to be fruitless. To encourage or necessitate a potentially wider inquiry would be a big step, and the fact that the search would nearly always be fruitless is not a positive thing.

CONCLUSIONS

385. My conclusions are:

i) The Defendants do not infringe because they are right about claim construction.

ii) It is conceded by Alexion that the Patent should be revoked on that claim construction.

iii) Had the Defendants infringed, then on the claim construction involved the Patent would have been invalid for obviousness over Tacken together with the documents to which it cross-refers.

iv) The other prior art attacks over Bowdish and Evans fail.

v) The insufficiency and lack of technical contribution attacks add nothing.

vi) I decline to decide the non-technical issues.

386. I will hear Counsel as to the form of Order if it cannot be agreed. I direct that time for seeking permission to appeal shall not run until after the hearing on the form of Order (or the making of such Order if it is agreed). I draw attention to paragraph 19.1 of the Patents Court Guide, which says that a hearing on the form of Order should take place within 28 days of hand down. In the present case, 28 days from hand down will be 17 June 2025.