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Datasheet for the decision of 20 September 2023

Case Number: T 1087/19 - 3.3.04

Application Number: 11001632.6

Publication Number: 2359834

IPC: A61K31/7105, A61K38/00, A61K39/395, A61P7/06

Language of the proceedings: EN

Title of invention:
Treatment of paroxysmal nocturnal hemoglobinuria patients by an inhibitor of complement

Patent Proprietor:
Alexion Pharmaceuticals, Inc.

Opponents:
O1: Amgen Inc.
O2: Hoffmann Eitle

Headword:
Treatment of PNH by inhibitor of complement / ALEXION PHARMACEUTICALS

Relevant legal provisions:
EPC Art. 100(b), 112a
EPC R. 106

Keyword:
Sufficiency of disclosure (no)
Obligation to raise objections - objection dismissed

Decisions cited:
T 0890/02

Catchword:
-

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Case Number: T 1087/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 20 September 2023

Appellant: (Patent Proprietor)	Alexion Pharmaceuticals, Inc. 100 College Street New Haven, CT 06510 (US)
Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Respondent I: (Opponent 1)	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 (US)
Representative:	Dörries, Hans Ulrich df-mp Fünf Höfe Theatinerstrasse 16 80333 München (DE)
Respondent II: (Opponent 2)	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastrasse 30 81925 München (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 13 February 2019 revoking European patent No. 2359834 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chair	L. Bühler
Members:	B. Claes
	B. Rutz

Summary of Facts and Submissions

I. The appeal lodged by the patent proprietor (appellant) lies from the decision of the opposition division revoking European patent No. 2 359 834 entitled "*Treatment of paroxysmal nocturnal hemoglobinuria patients by an inhibitor of complement*" and granted for European patent application No. 11001632.6, a divisional application of European patent application No. 07753249.7 filed under the PCT as an international patent application published as WO 2007/106585.

The sole claim of the granted patent reads:

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

II. The opposition division decided that the patent sufficiently disclosed the invention in the sole claim of the patent as granted (main request, Article 100(b) EPC), but that the claimed subject-matter lacked an inventive step (Articles 100(a) and 56 EPC).

III. With the statement of grounds of appeal, the appellant maintained the main request and submitted sets of claims of auxiliary requests.

IV. Both opponents (respondents I and II, respectively) replied to the appeal. The appellant and respondent I made further submissions.

V. The parties were summoned to oral proceedings and subsequently the board issued a communication pursuant to Article 15(1) RPBA providing the board's preliminary assessment of substantive and legal matters concerning the appeal. All parties made further submissions.

VI. After rescheduling the oral proceedings, the board issued a further communication pursuant to Article 15(1) RPBA. Both respondents filed submissions in response.

VII. During the oral proceedings, the appellant withdrew all auxiliary requests and raised the following objection under Rule 106 EPC in conjunction with Article 112a(2) EPC, presented in handwriting and containing the following text:

"*The Patentee is of the opinion that a procedural defect and a violation of the patentee's right to be heard has occurred.*

The OD decision clearly sets out in its reasoned decision a [sic] *paragraph 2.3.1 that the skilled person would immediately recognise that SEQ ID NO: 4 of the patent is an immature light chain and that the mature light chain would start at amino acid 23 of this SEQ ID NO: 4.*

Neither opponent challenged this finding of the OD in their response to the grounds of appeal.

Arguments were raised afresh at the oral proceedings themselves. A new argument raised at the oral proceedings before the Boards of Appeal does not provide the patentee with appropriate time to respond

to the objections raised. The arguments should not therefore have been admitted. The patentee therefore considers that this is a violation of its right to be heard under Art. 113 EPC."

At the end of the oral proceedings the Chair announced the decision of the board.

VIII. The following documents are referred to in this decision:

D1: US 2005/191298 A1

D17: US 6,355,245 B1

D38: Selected pages from Kabat *et al.* (1991), "*Sequences of Proteins of Immunological Interest*", U. S. Department of Health and Human Services (last printed version of the "Kabat" database).

D41: Alberts *et al.* (1994), Molecular Biology of the Cell, 3rd Edition, page 585.

IX. The appellant's arguments of relevance to the decision may be summarised as follows:

Ground for opposition under Article 100(b) EPC

Consideration of arguments in the proceedings

The argument that the signal peptide included in SEQ ID NO: 4 would not be present in eculizumab when producing a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 in transfected cells ("automatic cleavage" argument) had already been

on file in the opposition proceedings and was also submitted with the statement of grounds of appeal.

When replying to the statement of grounds of appeal, neither respondent had addressed the "automatic cleavage" argument, i.e. that transfection required conversion of the amino acid sequences SEQ ID NO: 2 and 4 into DNA, which required the skilled person to recognise that SEQ ID NO: 2 had no signal peptide whereas SEQ ID NO: 4 included such a signal peptide.

The respondents' new submissions on sufficiency of disclosure of the structure of eculizumab in relation both to (i) the "automatic cleavage" argument and to (ii) the fact that there was no information in the patent that eculizumab had a *kappa* light chain of a specific subgroup and that document D38 required analysis by a skilled person, had only been submitted during the oral proceedings. They should not be admitted into the proceedings or considered in the context of sufficiency of disclosure.

Sufficiency of disclosure

Eculizumab was the conventionally assigned non-proprietary name of the humanised monoclonal antibody in accordance with the World Health Organization's "International Nonproprietary Names (INN)" and had a defined sequence. The humanised monoclonal antibody eculizumab was however not available to the skilled person and the patent was the first disclosure of the amino acid sequence of its light and heavy chains and thus the first enabling disclosure for the skilled person to obtain this antibody.

The sequences of the heavy and light chains of eculizumab were disclosed in paragraph [0103] of the patent. Eculizumab comprised the heavy chain having the sequence SEQ ID NO: 2 and the *mature form* of the light chain of SEQ ID NO: 4.

The skilled person would immediately recognise, based on common general knowledge, that SEQ ID NO: 4 was erroneous and included a 22 amino acid N-terminal signal sequence which was not present in the mature antibody.

Signal peptides were known to be present at the N-terminus of immature (heavy and) light chain polypeptides upon expression.

Document D38 provided extracts from a database of biological sequences of proteins of immunological interest containing sequence alignments (the "Kabat" database) which evidenced the common general knowledge of the skilled person (see decision T 890/02). Document D38 depicted the signal peptides of various human light chains. Page 1 of the "Kabat" database in document D38 showed that the first three amino acid residues of the 22-residue signal peptides of the depicted human kappa light chains were predominantly MDM and the last two residues were predominantly RC. Also in SEQ ID NO: 4, the first three residues were MDM and residues 21 and 22 were RC. Furthermore, in all the human kappa light chain sequences depicted on pages 103 to 108 of the "Kabat" database in document D38, the sequence DIQM started the mature polypeptide. Residues 23 to 26 of SEQ ID NO: 4 were also DIQM, which the skilled person would recognise as being the start of the mature light chain of eculizumab.

Therefore the skilled person would recognise that SEQ ID NO: 4 was the amino acid sequence of the immature light chain that contained a signal peptide that was not present in the mature eculizumab antibody and would thus be in no doubt where the signal peptide featured in SEQ ID NO: 4.

The skilled person would produce eculizumab using cell-based recombinant methods, and not by artificially synthesising the polypeptide chains. To do so, the skilled person did not need guidance from the patent because it was known how to make antibodies. SEQ ID NO: 2 and SEQ ID NO: 4 and the sequences encoding these polypeptides provided recombinant means for producing eculizumab by providing expression cassettes and transfecting them into cells. These cells used to make eculizumab would then produce and process the mature protein chains for eculizumab because the signal peptide present in SEQ ID NO: 4 would be cleaved off in the endoplasmic reticulum (see document D41).

The skilled person did not need to know exactly where the signal peptide was located in SEQ ID NO: 4 because the expressing cell would automatically process the light chain of eculizumab. Verification of the antibody produced was thus also not required.

It was common general knowledge that expression of SEQ ID NO: 2 in cells should be carried out with a signal sequence.

The exemplified TRIUMPH trial disclosed in the patent provided evidence of the suitability of eculizumab for the medical use claimed.

X. The respondents' arguments of relevance to the decision may be summarised as follows:

Ground for opposition under Article 100(b) EPC

Consideration of arguments in the proceedings

The argument that the skilled person would not have immediately recognised that SEQ ID NO: 4 erroneously included the signal protein was already part of respondent I's appeal case, albeit filed in the reply to the appeal in the context of auxiliary request 2 filed with the statement of grounds of appeal.

Sufficiency of disclosure

It was neither immediately apparent to the skilled person that SEQ ID NO: 4, the light chain sequence of eculizumab, was erroneous nor what the correct sequence for the light chain of eculizumab was. In fact, there was no reason to assume that SEQ ID NO: 4 was incorrect.

The skilled person would not directly understand from the disclosure in the patent that the light chain of eculizumab started at position 23 of SEQ ID NO: 4. Indeed, SEQ ID NO: 2 was the correct final sequence of the heavy chain of eculizumab. The person skilled in the art would not have assumed that one sequence of the antibody did not include the signal peptide while the other sequence did include the signal peptide. Also, the patent clearly stated that the final antibody comprised both SEQ ID NO: 2 and SEQ ID NO: 4 (see paragraph [0018], final sentence). Thus, the immediate assumption would be that both sequences were sequences without signal peptide and, hence, the person skilled

in the art would not have been aware of an error in SEQ ID NO: 4 and would also not have been in a position to provide the correct information.

The "Kabat" database, of which selected pages of the last printed version (1991) had been filed as document D38, disclosed as a whole a huge amount of sequence information without indicating what could be derived therefrom. In order to arrive at conclusions or insights based on the sequence data, the skilled person was required to conduct an analysis of the data and the results of such analysis could thus not be considered to represent common general knowledge. The document could thus not support considerations on sufficiency of disclosure.

Document D38 only contained sequence information for human *kappa* light chains of *subgroup I*. However, the patent did not disclose that eculizumab used in the TRIUMPH trial comprised a kappa light chain. Therefore, the skilled person analysing the disclosure of the "Kabat" database, as last printed in 1991, as a whole would not have known to look specifically for information on the kappa light chains, let alone for such information limited to light chains of subgroup I. Furthermore, as the patent did not disclose the length of the signal peptide in SEQ ID NO: 4, the skilled person analysing the "Kabat" database as a whole or even the selected pages in document D38 needed to make the further assumption that the signal peptide had a length of 22 amino acids. The patent did not disclose this information. It was also immediately evident from page 1 of the "Kabat" database in document D38 that there were different signal peptide lengths within the selected subgroup I of the kappa light chain. Even if it were true that most (or all) human kappa light

chains of subgroup I started with the sequence DIQM, this was not a direct and unambiguous disclosure which would allow the skilled person to replace an erroneous description of an antibody in a patent disclosure.

Paragraph [0103] of the patent disclosed unambiguously that in eculizumab the heavy chain was of the sequence SEQ ID NO: 2 and the light chain was of the sequence SEQ ID NO: 4. However, such an antibody including a signal peptide in the light chain could hardly be expected to bind to C5 and one could therefore also not assume the same usefulness as shown in the TRIUMPH trial. Hence, its medical usefulness was questionable. There was indeed no example of this antibody in the patent or the art. Accordingly, only a limited assumption of sufficiency existed for the medical use of the antibody having the heavy chain of the sequence SEQ ID NO: 2 and the light chain of the sequence SEQ ID NO: 4 (see decision G2/21, points 74 and 77). There was thus a *prima facie* lack of "*plausibility*" for the medical application.

Claim 1 did not provide that eculizumab was produced in cells and also the patent did not disclose the production of eculizumab in a cellular environment. The patent only disclosed amino acid sequences, but not coding sequences which could be used for expression. Furthermore, in order to express the heavy and light chains of eculizumab based on their amino acid sequences, the skilled person had to realise that SEQ ID NO: 4 included a signal peptide, but SEQ ID NO: 2 did not. Providing the eculizumab used in the TRIUMPH trial on the basis of the patent thus amounted to an undue burden for the skilled person.

That it was possible to obtain eculizumab by expressing sequences in cells which automatically produced the correct chains was not the appropriate approach for assessing sufficiency of disclosure. In fact, even when following this approach, the skilled person would not be in a position to verify the correctness of the resulting antibody. There was also no evidence that the cells would always clip off the same 22 amino acids.

XI. The requests of the parties at the end of the oral proceedings were as follows:

The appellant requested that the decision under appeal be set aside and the oppositions be rejected (sole and main request, i.e. that the patent be maintained as granted).

The respondents requested that the appeal be dismissed.

Reasons for the Decision

Ground for opposition under Article 100(b) EPC

Consideration of arguments in the proceedings

1. When hearing the parties on sufficiency of disclosure, the appellant requested the board not to admit into the proceedings arguments on the part of the respondents that the skilled person would not have immediately recognised that SEQ ID NO: 4 erroneously included the signal protein.

2. However, these arguments were already part of respondent I's appeal case set out in the reply to the appeal (see paragraphs 213 to 231), albeit in the

context of auxiliary request 2 as filed by the appellant with the statement of grounds of appeal and in the context of added matter. In relation to the main request, it was disputed whether the denomination "eculizumab" in the claim referred to a single antibody and whether this antibody was identical to eculizumab disclosed in document D1 with reference to document D17 (see paragraph [0052] in document D1). In line with the decision under appeal, respondent I argued that the term "eculizumab" in the patent encompassed a range of anti-C5 antibodies, including the antibody disclosed in document D1. Based on this premise, respondent 1 would have contradicted itself in arguing that the patent did not enable the skilled person to produce eculizumab which was not further limited in the claim of the main request. On the other hand, the appellant relied for the main request on SEQ ID NO: 2 and SEQ ID NO: 4 as defining eculizumab and the argument that residues 1 to 22 of SEQ ID NO: 4 would be cleaved off during antibody production ("automatic cleavage" argument).

3. The amendment in claim 1 of auxiliary request 2 intended to further define the reference to eculizumab by the feature "wherein eculizumab comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of residues 23 to 214 of SEQ ID NO: 4". The amendment thus raised the question under Article 123(2) EPC as to whether the skilled person would directly and unambiguously derive from the disclosure of the application as filed a sequence missing the first 22 amino acids of SEQ ID NO: 4. It was also in this context that the appellant had reasoned their case based on document D38 in their statement of grounds of appeal. In view of the uniform concept of disclosure, there is no amendment of a party's case if factual allegations and arguments regarding the disclosure

which were part of a party's appeal case are later relied on when assessing the disclosure under a different legal provision.

4. Furthermore, the discussion on sufficiency of disclosure ensued from the appellant's submissions during oral proceedings in the context of inventive step. In this context the identity of the antibody "eculizumab" was a central issue (see point 2.). The appellant argued that eculizumab was an international non-proprietary name (INN) referring to a single antibody having a specific sequence and that it was immediately apparent to the skilled person that "eculizumab" was composed of the polypeptide of SEQ ID NO: 2 and the "mature" form of SEQ ID NO: 4, i.e. without the first 22 amino acid long signal peptide. The respondents' arguments presented in response thereto were the same as later presented under sufficiency of disclosure. The same is true for the appellant's arguments. Accordingly, the parties' submissions under sufficiency of disclosure and under inventive step were two sides of the same coin.

5. In view of the above circumstances, the board saw no reason not to consider such arguments to the extent that they had been put forward in the reply to the appeal in the context of added subject-matter for auxiliary request 2 and in the context of sufficiency of disclosure in the appeal proceedings.

Sufficiency of disclosure

6. The patent discloses the results of a clinical phase III study designated TRIUMPH (Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-

Controlled, using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (PNH)) which evaluated the effect of the humanised monoclonal antibody "eculizumab", directed against the terminal complement protein C5, on the stabilisation of hemoglobin levels and transfusion requirements during 6 months of treatment in a cohort of transfusion-dependent PNH patients as well as the assessment of measures of intravascular haemolysis and quality of life (see paragraphs [0003] and [0005] of the patent). The results presented demonstrate that certain aspects of quality of life were improved by the treatment of PNH patients with eculizumab independent of transfusion (see paragraph [0006] and the presentation of the results in the section of the patent headed "EXEMPLIFICATION").

7. The invention thus pertains to the treatment of a patient afflicted with PNH by administering the humanised monoclonal antibody designated eculizumab and, accordingly, the claimed subject-matter is a particular eculizumab single-use dosage form composition for use in the treatment of PNH (see section I.).

8. The patent must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (see Article 100(b) EPC). In accordance with established case law of the Boards of Appeal in respect of further medical use claims, this means with respect to the invention as defined in the claim, that the following needs to be established:

(1) the skilled person must be able, based on the disclosure in the patent and/or common general knowledge, to obtain the antibody eculizumab disclosed

in the patent, and

(2) the skilled person must find it credible, based on the evidence in the application as filed and/or common general knowledge, that the claimed therapeutic effect, i.e. the treatment of paroxysmal nocturnal hemoglobinuria (PNH), can be achieved.

9. The appellant emphasised repeatedly that eculizumab was the conventionally assigned non-proprietary name for the humanised monoclonal antibody in accordance with the nomenclature used in the World Health Organization's "International Nonproprietary Names (INN)" (see also point 4.). This eculizumab was used in the TRIUMPH trial disclosed in the patent. The same was also true for the antibody designated eculizumab referred to in the state of the art, e.g. in document D1. The patent was however the first disclosure of the amino acid sequence of the light and heavy chains of the humanised monoclonal antibody eculizumab and the first enabling disclosure for the skilled person to obtain this antibody.

10. The board agrees with the appellant that eculizumab used in the TRIUMPH trial disclosed in the patent refers to a particular humanised monoclonal antibody having a designation following the INN nomenclature. Indeed, any other interpretation of the term would render the results obtained by the trial and disclosed in the patent nonsensical and thus not useful in a possibly required assessment as to whether it was credible to the skilled person that eculizumab achieved the claimed therapeutic effect (treatment of a patient afflicted with PNH; see item (2) above in point 8.).

11. Accordingly, it needs to be established whether the skilled person was able, based on the disclosure in the patent and common general knowledge, to obtain the humanised monoclonal antibody eculizumab of the patent and used in the TRIUMPH trial (see item (1) above in point 8.). Both the opposition division and the appellant held this as given, whereas the respondents held this to require an undue burden.

12. The patent defines in paragraph [0103] the sequences of the heavy chain, i.e. SEQ ID NO: 2, and the light chain, i.e. SEQ ID NO: 4, of the antibody eculizumab. Likewise, in paragraph [0018] the patent discloses an antibody with a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 (see last sentence). However, it is undisputed that the 236 amino acid long SEQ ID NO: 4 erroneously includes at its N-terminal end the sequence of a 22 amino acid long signal peptide which is not included in the mature humanised monoclonal antibody eculizumab. Accordingly, despite the unequivocal statements in the patent, the eculizumab antibody used in the TRIUMPH trial is in fact composed of a heavy chain of the sequence SEQ ID NO: 2 but *not* a light chain of the sequence SEQ ID NO: 4.

13. It must thus be concluded that the skilled person, when attempting to rework the claimed invention based on the disclosure in the patent, would fail to obtain the eculizumab antibody used in the TRIUMPH trial. This fact alone should in principle provide justification for the patent being assessed as not providing sufficient disclosure the claimed invention, *unless* however, the technical disclosure in the patent could nevertheless, in particular having regard to common

general knowledge, teach the skilled person the correct sequences of the heavy and light chain of eculizumab.

14. Relying on common general knowledge, the appellant has essentially submitted two lines of argument defending the position that the patent enabled the skilled person to obtain the very eculizumab antibody disclosed in the patent and used in the TRIUMPH trial.

15. In a first line of argument, the appellant held that, based on common general knowledge, the skilled person would immediately recognise that SEQ ID NO: 4 was erroneous and included the 22 amino acid N-terminal signal sequence which was not present in the mature antibody. When reworking the invention, the skilled person would thus use the *mature form* of the light chain disclosed in SEQ ID NO: 4 as the light chain of eculizumab.

16. By way of introduction, the board is able to agree in this context with the appellant that it was common general knowledge that antibodies in general are secreted proteins produced from precursor light and heavy chain polypeptides in cells, which precursors each comprise a signal peptide and a mature polypeptide. The signal peptides are cleaved off in the endoplasmic reticulum (ER) of the expressing cell and the mature polypeptide then folds to form the mature protein chain.

17. On a more specific level the appellant further submitted, however, that the skilled person would have no doubt that SEQ ID NO: 4 is the amino acid sequence of the *immature* light chain which included a signal peptide that was not present in mature eculizumab and that residue 23 in SEQ ID NO: 4 was in fact the N-

terminal amino acid of the mature light chain of eculizumab, based on common general knowledge as represented by the "Kabat" database, of which selected pages from the last printed version (1991) were on file as document D38. The "Kabat" database was a known database of biological sequences of proteins of immunological interest and sequence alignments. In decision T 890/02 (OJ EPO 2005, 497), it was established that such a database could represent the common general knowledge of the skilled person as defined in the case law. The selected pages of the "Kabat" database in document D38 showed the signal peptides of various human kappa light chains of known antibodies. The skilled person could take herefrom that, as was true of SEQ ID NO: 4, (a) the first three residues of the 22-residue signal peptides of the depicted human kappa light chains were predominantly (10/12) MDM and the last two residues were predominantly (10/12) RC (see attached page 1), and (b) as with residues 23 to 26 of SEQ ID NO: 4, the sequence DIQM started the mature light chain polypeptide in all human kappa light chain sequences depicted in document D38.

18. This line of argument from the appellant essentially reflects the submissions in the opposition proceedings which had convinced the opposition division that eculizumab was sufficiently disclosed (see section II.). The opposition division decided that "[S]*ince no proof of the contrary is available, the OD can see no reason not to accept P's argument concerning the fact that the skilled person would recognize that the SEQ ID NO: 4 is the immature light chain of eculizumab and that the mature light chain would/should start at amino acid 23 of this sequence. Hence it is the OD's view*

that the patent discloses enough information for a skilled person to produce an eculizumab protein.".

19. The board cannot, however, concur with the opposition division's decision that the patent discloses enough information for a skilled person to produce an eculizumab antibody disclosed in the patent and used in the TRIUMPH trial, or with the appellant that this is given based on the disclosure in the patent and having regard to common general knowledge, but rather agrees with the respondents that it was neither (i) immediately apparent to the skilled person that SEQ ID NO: 4 for the light chain sequence of eculizumab was erroneous nor (ii) clear to the skilled person that the sequence included a 22 amino acid long signal peptide or what the correct sequence for the light chain of eculizumab should be.

20. In respect of aspect (i), the board concurs with the respondents that there appears to be no reason for the skilled person, when considering the disclosure in the patent, to assume that SEQ ID NO: 4 is incorrect in the first place. Indeed, the board is not convinced that the statement "*SEQ ID NO: 4 - Eculizumab Light chain*" in paragraph [0103] of the patent with reference to the depicted 239 amino acid sequence, that sequence as such, or the disclosure in paragraph [0018] (see last sentence) of the patent of an "antibody" with a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 constituted such an apparent and obvious error that a skilled person would doubt whether this information was correct. On the contrary, the skilled person would accept these statements as correct without giving them a second thought.

21. Indeed, the board has seen no convincing arguments as to why the skilled person, when confronted with this disclosure, would *prima facie* be alerted and consequently prompted to consider and analyse the corresponding sequence depicted in SEQ ID NO: 4 with a view to determining the presence of particular functional parts/compounds in the unannotated amino acid sequence, here an ER signal peptide sequence. Furthermore, even on closer examination of the sequence of SEQ ID NO: 4, the skilled person would not, as the appellant alleged, *immediately* recognise that the depicted sequence of SEQ ID NO:4 contained an error, but rather could, at best, be led to doubt that the depicted sequence was the sequence it purported to represent. This state of doubt, however, does not equate to the skilled person having no doubt that the depicted sequence was erroneous and could not be meant to read as such, i.e. immediately recognising that it was erroneous. In addition, the board also agrees with the respondents that the skilled person would not have assumed or expected that one depicted sequence of a chain of eculizumab in the patent included the signal peptide while the other did not, all the more so because the patent explicitly refers in [0018] to an antibody "*which comprises a heavy and a light chain, wherein the heavy chain consists of SEQ ID NO: 2 and the light chain consists of SEQ ID NO: 4*".

22. In respect of aspect (ii), the board also agrees with the respondents that the skilled person, even on closer examination of the sequence of SEQ ID NO: 4, would not directly have understood from the disclosure in the patent, even having regard to common general knowledge, that the light chain of eculizumab used in the TRIUMPH trial did not include the first 22 amino acid long

signal peptide but started at position 23 of SEQ ID NO: 4.

23. The board agrees with the appellant with reference to decision T 890/02 that databases may be considered to represent common general knowledge for the skilled person under certain circumstances.

24. Indeed, in the case underlying the decision T 890/02, the competent board had to decide whether the skilled person wanting to find the nucleotide sequence of a certain gene mentioned in a document would have looked for and found this information in well-known and accessible databases (here ENZYME and the EMBL Nucleotide Sequence databases; see Reason 6). The board confirmed in the particular case that from the given name or corresponding EC number of a particular enzyme, the skilled person could retrieve complete information on properties as well as amino acid sequences and nucleotide sequences of the corresponding genes (see Reasons 7 and 8). The board decided that these databases could represent common general knowledge because they fulfilled the three criteria set out in the case law when defining common general knowledge, i.e. (a) they were known by the skilled person as an appropriate source for obtaining the desired information, (b) looking for this information required no undue effort since no search strategy was needed (but only the EC number or the enzyme name) and (c) the information retrieved (here the nucleotide sequence) did not need any further research work, i.e. it was unambiguous and straightforward (see Reason 9).

25. Similar to the databases referred to in decision T 890/02, the "Kabat" database as a whole, of which selected pages of the last printed version of 1991 are

on file as document D38, provides a huge amount of sequence information (database) on biological sequences of proteins of immunological interest (antibodies), including signal sequences of light and heavy chains of antibodies (see page iii, table of contents, included in document D38, sections covering pages 1 to 44) and variable region light chain sequences (see page iii, table of contents, included in document D38, sections covering pages 103 to 150).

26. The "Kabat" database can in principle be used by the skilled person to retrieve data relating to a particular sequence based on appropriately defined queries. However, in the present case, it is not a single sequence which is sought, for example by searching for the sequence of the signal peptide of "HK101'CL" (see page 1 included in document D38). Rather, the appellant's arguments relating to the "Kabat" database and document D38 referred to in point 17. above require, on the contrary, the factual retrieval of selected information of a certain (statistical) quality which goes substantially beyond the use of the database in the case underlying decision T 890/02. The circumstances of the case in hand thus differ substantially from those in case T 890/02. The "Kabat" database can therefore not be accepted as complying with the requirements that (a) the database was known as an appropriate source for obtaining this information, (b) finding the information required no undue effort beyond a defined query, and (c) the retrieved information was unambiguous and straightforward as established in the case law defining common general knowledge. Accordingly, for this reason alone, the board cannot accept the information retrieved by the appellant in document D38 or indeed

the "Kabat" database itself as a whole as representing the common general knowledge of the skilled person.

27. Furthermore, and for the sake of completeness, the board agrees with the respondents from a technical point of view that the appellant's arguments relating to document D38 referred to in point 17. above, i.e. that the skilled person would *immediately* realise that SEQ ID NO: 4 included a 22 amino acid long signal peptide and the mature eculizumab light chain thus started at position 23, are not persuasive. In fact, the included selected pages in document D38 only depict sequence information for human *kappa* light chains of *subgroup I*. However, the patent does not disclose that eculizumab used in the TRIUMPH trial in fact comprises a kappa light chain. Therefore, the skilled person analysing the disclosure in light of the "Kabat" database as a whole would not have known to look specifically for information on kappa light chains, let alone light chains of subgroup I. Moreover, as the patent does not disclose any particular length of any signal peptide purportedly present in SEQ ID NO: 4, the skilled person analysing the "Kabat" database as a whole, or even the selected pages submitted on file in document D38, needed to make the further assumption, in the absence of any pointer, that the signal peptide had a length of 22 amino acids. Moreover, it is immediately evident from page 1 of the database included in document D38 that there are different signal peptide lengths within the selected subgroup I of the kappa light chain.

28. Therefore, in order to arrive at insights and conclusions on the disclosed sequence data, the skilled person was required to conduct an in-depth analysis of the data. The results of such an analysis cannot,

contrary to the appellant's argument, be considered to represent common general knowledge.

29. In a second line of argument, the appellant held that, in order to rework the claimed invention based on common general knowledge, the skilled person would produce the antibody eculizumab using cell-based recombinant methods. Such antibody-producing cells would then produce and process the mature protein chains for eculizumab because the signal peptide present in SEQ ID NO: 4 would be cleaved off in the endoplasmic reticulum (see document D41). It was also common general knowledge that expression of SEQ ID NO: 2 in cells should be carried out with a signal sequence. It was thus not necessary for the skilled person to know exactly where the signal peptide was located in SEQ ID NO: 4 as it would automatically be cleaved off by the cell. Verification of the antibody produced was thus not required.

30. The board agrees with the respondents, however, that the claim does not specify that eculizumab is to be produced in cells. Furthermore, the patent only discloses amino acid sequences for the light and heavy chains of eculizumab, at the same time omitting any reference to coding sequences useful for the expression of such chains. In the board's judgement, it is therefore already questionable whether the required processing of the mature chains of eculizumab during cellular expression as argued by the appellant is disclosed in and is thus also part of the technical teaching of the patent.

31. Furthermore, sufficiency of disclosure of the eculizumab antibody used in the disclosed TRIUMPH trial cannot be acknowledged based on an alleged corrective

downstream processing of specifically disclosed amino acid sequences of the light and heavy chains, in particular SEQ ID NO: 4, which the patent actually teaches to be part of the eculizumab antibody (see point 12.). Indeed, the required reference to such downstream processing illustrates, in fact, a wish on the part of the appellant to *repair* the defective disclosure of the patent concerning the eculizumab antibody used in the disclosed TRIUMPH trial.

32. In view of the above considerations the board concludes that, based on the disclosure in the patent and having regard to common general knowledge, the skilled person would fail to obtain the eculizumab antibody used in the TRIUMPH trial with the correct sequences of the heavy and light chains. Accordingly, the patent does not sufficiently disclose the claimed invention and the ground for opposition under Article 100(b) EPC prejudices maintenance of the patent as granted.

Objection under Rule 106 EPC in conjunction with Article 112a(2) EPC

33. During the oral proceedings, the appellant raised an objection under Rule 106 EPC in conjunction with Article 112a(2)(c) EPC (see section VII.).

34. The objection concerns the board's decision (see points 1. to 5.) to admit and consider arguments from the respondents allegedly filed for the first time during the oral appeal proceedings. In the appellant's view, "*A new argument raised at the oral proceedings before the Boards of Appeal does not provide the patentee with appropriate time to respond to the objections raised. The arguments should therefore not be admitted.*"

35. However, neither during the hearing on the admittance of particular arguments from the respondents into the proceedings, nor on any other occasion prior to submitting the text of the objection under Rule 106 EPC, did the appellant notify the board or express a need for more time to appropriately prepare pertinent submissions or request a corresponding adjournment of the oral proceedings. Nor did the appellant request an opportunity to discuss and consider any of the documents filed with their statement of grounds of appeal.

36. The board accordingly only dealt with the appellant's non-admittance requests in the form as submitted and argued during the oral proceedings and started subsequently from the premise that in the course of the further hearing on sufficiency of disclosure, in the absence of corresponding notifications from the appellant to the contrary, the appellant's pleadings were complete. The board does not consider this course of proceedings to constitute a violation of the appellant's right to be heard under Article 113(1) EPC.

37. Therefore, the objection under Rule 106 EPC in conjunction with Article 112a(2) EPC was dismissed.

Order

For these reasons it is decided that:

1. The objection under Rule 106 EPC is dismissed.

2. The appeal is dismissed.

The Registrar: The Chair:

I. Aperribay L. Bühler

Decision electronically authenticated