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Datasheet for the decision of 22 April 2021

Case Number: T 0033/19 - 3.3.04

Application Number: 15152757.9

Publication Number: 2894165

IPC: C07K16/18

Language of the proceedings: EN

Title of invention:
Methods and compositions for treating complement-associated disorders

Applicant:
Alexion Pharmaceuticals, Inc.

Headword:
Eculizumab for use in treating aHUS/ALEXION

Relevant legal provisions:
EPC Art. 56, 83, 111(1) sentence 2
RPBA Art. 11, 12(2)

Keyword:
Sufficiency of disclosure - (yes)
Inventive step - reasonable expectation of success (no)
Appeal decision - remittal to the department of first instance (yes)

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Case Number: T 0033/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 22 April 2021

Appellant: (Applicant)	ALEXION PHARMACEUTICALS, INC. 352 Knotter Drive Cheshire, CT 06410 (US)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 2 August 2018 refusing European patent application No. 15 152 757.9 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairman	B. Claes
Members:	A. Schmitt
	M. Blasi

Summary of Facts and Submissions

I. The appeal of the applicant ("the appellant") lies from the decision of the examining division refusing European patent application No. 15 152 757.9 ("the application") entitled "*Methods and compositions for treating complement-associated disorders*".

II. In its decision, the examining division held that the application did not disclose the invention as defined in the claims of the main request in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC), and refused the application for this sole reason.

III. With the statement of grounds of appeal, the appellant re-submitted the set of claims on which the decision under appeal was based (main request) and submitted two documents (hereafter numbered D15 and D16).

Claim 1 of the main request reads:

"1. An antibody for use in treating atypical hemolytic uremic syndrome (aHUS) in a patient, wherein the antibody is eculizumab."

Claims 2 and 3 are dependent on claim 1.

IV. The board issued a summons to oral proceedings as requested by the appellant, together with a communication pursuant to Article 15(1) RPBA in which the board provided its preliminary opinion that the application as amended met the requirements of Article 83 EPC, but the claimed subject-matter lacked inventive step (Article 56 EPC).

V. In response to the board's communication, the appellant, by letter dated 13 April 2021, submitted three documents which had been cited in document D12 (numbered hereafter R55, R67 and R69), and provided arguments in favour of inventive step of the claimed subject-matter.

VI. At the request of the appellant oral proceedings were held by videoconference. At the end, the chair announced the board's decision.

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

D2 Gruppo *et al*. (2009), N. Engl. J. Med. 360(5), 544-6

D4 Würzner and Zimmerhackl (2006), in: Complement and Kidney Disease, edited by Peter F. Zipfel, Birkhauser Verlag Basel/Switzerland, 149-63

D5 Loirat *et al*. (2008), Pediatr. Nephrol. 23, 1957-72

D6 Kavanagh *et al*. (2008), Annu. Rev. Med. 59, 293-309

D12 Ricklin and Lambris (2007), Nature Biotechnology 25(11), 1265-75

D15 Nuernberger *et al*. (2008), Blood 112, 2294 http://www.bloodjournal.org/content/112/11/2294

D16 EMEA product characteristics eculizumab

R55 Avant Immunotherapeutics, Inc. Press Release, (2007)

R67 Armstrong, J. (2007), Am. Med. Assoc. 297(1), 43-51

R69 Mitchell (2007), http://www.upi.com/Health_Business/Analysis/2007/01/02/analysis_alexions_pexelizumab_fails/6113/

VIII. The appellant's arguments, as far as relevant to the decision, are summarised as follows.

Main request

Sufficiency of disclosure (Article 83 EPC)

The application described the amelioration of specific aHUS symptoms following the administration of eculizumab (page 16, lines 7 to 12), and provided exemplary dosing schedules on pages 21 to 24. Further, the association between aHUS and the complement system was detailed in the application, this being in line with the common general knowledge as evident from the review articles D5 and D6, which disclosed the role of the complement alternative pathway in the pathogenesis of aHUS. The claimed subject-matter was thus based on the rationale that aHUS was a complement-associated disorder and eculizumab targeted a component of the complement system. The claimed technical effect (treatment of aHUS with eculizumab) was thus plausible from the application as filed.

In the case at hand, there was no reason to doubt the credibility of the disclosure on page 16 of the

application, which singled out three specific symptoms of aHUS and recited that they were ameliorated after treatment with eculizumab. Documents D2, D15 and D16, all published after the priority date of the application, confirmed this result. Moreover, documents D2 and D15 substantiated the statement on page 16 of the application that the applicant had performed clinical trials before the priority date of the application.

However, since the technical effect was plausible from the teaching of the application as a whole and the common general knowledge represented by documents D5 and D6, which disclosed the involvement of the complement alternative pathway in aHUS, it was not necessary to rely on the cited passage on page 16 of the application.

Consequently, there were no serious doubts substantiated by verifiable facts that the claimed technical effect was not achieved. The requirements of Article 83 EPC were thus met.

Inventive step (Article 56 EPC)

Claim 1

Documents D4, D5 and D6 did not provide the skilled person with a reasonable expectation that aHUS could successfully be treated with eculizumab since these documents merely disclosed the involvement of the complement system in aHUS. The suggestion to treat aHUS with anti-C5 antibodies was mere speculation based solely on this association and not on any experimental data (document D4, page 160, last sentence; document D5, page 1966, paragraph bridging left-hand

and right-hand column; document D6, page 304, right-hand column, first paragraph). The complement cascade was a complex system with multiple separate pathways (document D12, Figure 2), and thus purely mechanistic association of the complement system with a disease, as was the case for aHUS, could not lead to a reasonable expectation of success.

According to document D6, the exact target of the complement system for an intervention in aHUS was not clear and no testing had yet been performed in an aHUS animal model (document D6, page 304, right-hand column, first paragraph).

Attempts to treat other complement-associated disorders with complement-targeting agents had failed (document D4, page 159, second paragraph; document D12, page 1269, right-hand column, first paragraph; document R55, page 1270, right-hand column, last paragraph to page 1271, first paragraph, and documents R67 and R69, all three cited in document D12).

Notably, document D4 suggested the anti-C5 antibody pexelizumab for treating aHUS (sentence bridging pages 159 and 160), but this turned out to be ineffective in treating other complement-associated disorders despite promising pre-clinical results (document D12, page 1270, right-hand column, last paragraph and page 1271, first paragraph). It was thus not predictable whether a complement-associated disease could be treated with a complement inhibitor.

Consequently, the suggestion to try treating aHUS with an anti-C5 antibody based solely on a mechanistic rationale, as was the case in documents D4, D5 and D6, could not lead to a reasonable expectation of success

for the skilled person. At most, it would lead to the skilled person hoping to succeed, but this was not sufficient to deny inventive step. The claimed subject-matter thus involved an inventive step as regards the disclosure of documents D4, D5, D6 and D12.

IX. The appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division for consideration of novelty and inventive step.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is admissible.

Main request

Sufficiency of disclosure (Article 83 EPC)

2. The board considers the requirement of sufficiency of disclosure under Article 83 EPC to be fulfilled with respect to a claim for a second medical use if (a) the disclosure in the application, supplemented by the common general knowledge, enables the skilled person to obtain the compound and to use it for the claimed indication, and (b) the application discloses the suitability of the product to be manufactured for the claimed therapeutic application unless this is already known to the skilled person at the priority date (see also Case Law of the Boards of Appeal, 9th edition, 2019, II.C.7.2).

3. Compliance with the first requirement had not been questioned in the decision under appeal. The examining

division however held that the second requirement was not met, i.e. that there was no evidence that treatment of aHUS could be achieved with eculizumab.

4. The examining division considered that while there were "*some indications in the common knowledge to go for C5 inhibition*", this was "*still speculative*" (point 5.1.2.1 of the decision). Further, the examples disclosed in the application concerning the treatment of aHUS were "*of a prophetic nature*" (point 5.1.2.2 of the decision) and the passage cited by the appellant on page 16, lines 7 to 12 was "*a simple verbal statement*" (ibid.). The examining division concluded that "*the technical teaching of the application as filed does not go beyond what was provided in the common general knowledge at the time of filing*" and that "*the cause effect-relationship* [sic] *was not made plausible in the application as originally filed*" (ibid.). Further, no clear cause-effect relationship between complement factor C5 and aHUS was known from the prior art (point 5.1.2.3).

5. The board notes that the application does not demonstrate experimentally that the claimed therapeutic effect can be achieved. However, experimental evidence is not a prerequisite for establishing sufficiency of disclosure of a patent application if the skilled person has no reason to doubt that treatment with the claimed agent, here eculizumab, can achieve the therapeutic effect necessary in the treatment of the claimed disease, here aHUS, with due regard to the common general knowledge.

6. The application identifies aHUS as a complement-associated disorder (page 9, lines 3 to 5) and discloses that the C5-inhibitory antibody eculizumab

should be administered to aHUS patients for the treatment of aHUS symptoms (page 16, lines 7 to 12, Examples 1 and 2).

7. Documents D4, D5 and D6 can be considered to reflect the common general knowledge of the skilled person regarding the etiology of aHUS and its implication for effective therapeutic approaches targeting the complement system.

8. Document D4, published in 2007, reviews therapeutic strategies for atypical and recurrent HUS. It discloses that the complement system is involved in 50 to 70% of aHUS patients (page 150, last sentence of the first paragraph), and that humanised versions of human C5-blocking antibodies have been generated. One of these, pexelizumab, has reached clinical trials and "*may represent an interesting therapy option for patients suffering from aHUS*" (page 160, first two lines). Document D4 concludes that "[*h*]*opefully, new insights in the mechanism of disease and perhaps new complement inhibitors (such as humanised anti C5 antibodies) may improve treatment and outcome of these poor patients*" (last four lines on page 160).

9. Document D6, published online in 2007, discloses that the complement alternative pathway "*plays a key role in the pathogenesis of aHUS*" (page 294, right-hand column, last line) and reviews the involvement of mutations in complement regulatory genes in aHUS, available aHUS mouse models and therapeutic considerations. With respect to complement-inhibitor therapies, it is suggested that "*the use of antibodies against key activating components of complement; for example C5 should have beneficial effects in ameliorating the downstream damage mediated by the anaphylatoxin C5a and*

preventing the formation of a membrane attack complex on host cell surfaces" (page 304, right-hand column, first paragraph). Document D6 further reports that preventing C5 activation in factor H (FH) knock-out mice ameliorated spontaneous and experimental glomerulonephritis, and suggests testing this approach in an FH transgenic mouse which develops aHUS (*ibid.*).

10. Document D5, published in 2008, is a further review article describing aHUS as a disorder of the complement alternative pathway associated with mutations in complement regulatory proteins (page 1959 *et seq.*) and characterised by excessive liberation of C3 cleavage fragments and the formation of the C5b9 complex (Figure 1, paragraph bridging columns 1 and 2 of page 1961). Document D5 also discusses different aHUS treatment options (page 1964 *et seq.*) and discloses that "*[m]onoclonal humanized antibodies against key activating components of complement such as C5 should be beneficial, by decreasing the damage mediated by the anaphylatoxin C5a and preventing the formation of the membrane attack complex on cell surfaces*" (paragraph bridging columns 1 and 2 on page 1966).

11. The documentary evidence referred to above demonstrates that aHUS was generally known in the art as a disorder of the complement system, as also described in the application. Further, complement inhibitors and specifically anti-C5 antibodies were known to the skilled person as possible therapeutic options for aHUS based on the deregulation of the complement alternative pathway in aHUS and the availability of such inhibitory C5 antibodies. Based on this evidence, the board is satisfied that the skilled person, having regard to the common general knowledge reflected in this documentary evidence, had no reason to question that treatment with

eculizumab could achieve the therapeutic effect necessary in the treatment of aHUS.

12. In view of the above considerations, the board judges that the application, with due regard to the common general knowledge, discloses the suitability of eculizumab for achieving the therapeutic effect necessary in the treatment of aHUS and thus the claimed invention.

13. Accordingly, the board holds that the application with this set of claims meets the requirements of Article 83 EPC. The appeal is therefore allowable.

Inventive step (Article 56 EPC)

Claim 1

14. In the case at hand, the board assessed inventive step of the claimed subject-matter with regard to the disclosures in documents D4 to D6 and document D12.

Closest prior art and objective technical problem

15. The claim is directed to the use of the antibody eculizumab in treating atypical hemolytic uremic syndrome (aHUS) in a patient.

16. Document D4 (page 152 to 153, Figure 2), document D5 (page 1964, right-hand column, second paragraph) and document D6 (page 303, right-hand column, second paragraph) all disclose current aHUS therapy strategies such as e.g. plasma exchange or plasma infusions. Each of these known aHUS therapies disclosed in these documents constitutes a suitable starting point for assessing inventive step.

17. The claimed subject-matter differs from these known aHUS therapies in that the C5-inhibitory antibody eculizumab is used.

18. The board has not seen, nor been presented with, comparative data for the known and the claimed therapies. Hence no special technical effect can be associated with the particular use of eculizumab. The objective technical problem can therefore be formulated as the provision of an alternative therapeutic for treating aHUS.

19. As outlined above in the context of sufficiency of disclosure, documents D4, D5 and D6 disclose the involvement of the alternative pathway of the complement system in aHUS and, based on this association, suggest investigating anti-C5 antibodies as a therapeutic option for treating aHUS (see points 7. to 11. above).

20. However, these suggestions are not based on treatment-related data of *in vitro* or *in vivo* experiments, and equally express uncertainty as to the outcome of the suggested treatment. Indeed, in document D4 it is considered that the anti-C5 antibody pexelizumab "*may represent an interesting therapy option*" (page 160, lines 1 to 2) and it is concluded that "*perhaps new complement inhibitors (such as humanized anti C5 antibodies) may improve treatment and outcome* [of aHUS patients]" (page 160, last sentence). Document D5 considers that "[*m*]*onoclonal humanized antibodies against key activating components such as C5 should be beneficial*" (page 1966, paragraph bridging left-hand and right-hand column). Document D6 confirms that no C5-inhibitory antibody had yet been tested in an aHUS

animal model (page 304, right-hand column, first paragraph).

21. Thus, while the disclosure of these documents provided the skilled person with an incentive to investigate whether an anti-C5 antibody could treat aHUS, it cannot be considered to provide the skilled person with a reasonable expectation that aHUS could successfully be treated with eculizumab.

22. For the sake of completeness, the board notes that the same conclusion is reached when considering the disclosure in document D12, a scientific review of complement-targeted therapies. In particular, document D12 discloses that eculizumab is a therapeutic agent for paroxysmal nocturnal hemoglobinuria and has undergone (pre-)clinical trials for a variety of conditions, which however do not include aHUS (Table 1 and pages 1270 to 1271). Further, while the document mentions the involvement of mutations in complement factor genes in aHUS (page 1268, left-hand column, first paragraph), it does not discuss any therapies for aHUS, and hence does not suggest to the skilled person that aHUS too could be treated with eculizumab.

23. The board concludes that none of documents D4, D5, D6 and D12 provides the skilled person with a reasonable expectation that aHUS could successfully be treated with eculizumab.

24. Although the application lacks experimental data, it discloses on page 16, lines 7 to 12 that "*the inventors have discovered that hypertension, reduced urine output, and low platelet levels are ameliorated in eculizumab-treated aHUS patients in less than one month (e.g., less than two weeks) from initiating chronic*

treatment with eculizumab". The board has no reason to doubt that the amelioration of the indicated aHUS symptoms within the indicated time span has been observed by the inventors. Furthermore, documents D2, D15 and D16, all published after the priority date of the application, back up this teaching which is derivable from the application.

25. Consequently, the board holds that the application as filed provides a contribution going beyond the disclosure of the prior art in that it discloses that particular aHUS symptoms are ameliorated after administering eculizumab, i.e. that aHUS can be treated with eculizumab.

26. In light of the above considerations, the board considers the claimed subject-matter to involve an inventive step when only considering the disclosure in documents D4, D5, D6 and D12.

Remittal (Article 111(1) EPC)

27. Pursuant to Article 111(1), second sentence, EPC, the board may either exercise any power within the competence of the department which was responsible for the decision appealed or remit the case to that department for further prosecution.

28. Pursuant to Article 11 RPBA 2020, the board shall not remit a case to the department whose decision was appealed for further prosecution, unless special reasons present themselves for doing so.

29. In the present case, the sole reason for refusing the application was that it did not meet the requirements

of Article 83 EPC, and the board has reviewed this decision (see points 2. to 13. above).

30. Furthermore, the board also assessed whether or not the claimed invention involved an inventive step, taking into account the disclosure of the same documents analysed for the assessment of sufficiency of disclosure, for the reason that it considered this not to open up any fields of discussion raised for the first time at the appeal stage (see point 14. above).

31. The examining division, in the decision under appeal, did not express an opinion on the patentability of the claimed invention having regard to the disclosure of all the documents cited during the examination proceedings.

32. Thus the board would have to deal with a number of fresh aspects unrelated to the issues addressed in the decision under appeal. As confirmed by Article 12(2) RPBA 2020, it is the primary object of the appeal proceedings to review the decision under appeal in a judicial manner (see also Case Law of the Boards of Appeal, 9th edition 2019, section V.A.1.1, second paragraph and decisions referred to there). Furthermore, the appellant has requested that the case be remitted to the examining division for consideration of novelty and inventive step as its main procedural request. The board thus considers that special reasons present themselves for remitting the case to the examining division.

33. Accordingly, exercising its discretion under Article 111(1), second sentence, EPC, the board decided to remit the case to the examining division for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division for further prosecution.

The Registrar: The Chair:

I. Aperribay B. Claes

Decision electronically authenticated