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Datasheet for the decision of 22 April 2021

Case Number: T 0096/20 - 3.3.04

Application Number: 16179565.3

Publication Number: 3101031

IPC: C07K16/18, A61K39/395, A61K38/00, A61P21/04

Language of the proceedings: EN

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

Applicant:
Alexion Pharmaceuticals, Inc.

Headword:
Treatment of myasthenia gravis/ALEXION

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:
T 0239/16

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Case Number: T 0096/20 - 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. 100 College Street New Haven, CT 06510 (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 19 June 2019 refusing European patent application No. 16179565.3 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. 16 179 565.3 ("the application") entitled "*Methods and compositions for treating complement-associated disorders*".

II. The examining division held that claims 1 to 9 of the main request did not meet the requirements of Article 123(2) EPC and that the subject-matter of claim 1 of auxiliary request 1 did not meet the requirements of Article 56 EPC.

III. With the statement of grounds of appeal, the appellant submitted sets of claims of a main request and an auxiliary request 1, with the main request identical to auxiliary request l and auxiliary request l identical to the main request on which the decision under appeal was based, and, *inter alia*, argued in favour of inventive step.

IV. The board summoned the appellant to oral proceedings, as it had requested, and subsequently issued a communication pursuant to Article 15(1) RPBA in which it, *inter alia*, provided its preliminary opinion with respect to inventive step of the subject-matter of claim 1 of both requests.

V. In response to the board's communication, the appellant submitted by letter dated 13 April 2021 sets of claims of further auxiliary requests 1 and 3 and four documents (numbered hereafter D11 to D14). The auxiliary request submitted with the statement of

grounds of appeal was renumbered as auxiliary request 2.

Claim 1 of the main request and auxiliary request 1 thus reads:

"1. An inhibitor of human complement component C5 for use in treating myasthenia gravis (MG) in a human, wherein the inhibitor is an anti-C5 antibody."

Claim 1 of each of auxiliary requests 2 and 3 thus reads:

"1. Eculizumab for use in treating myasthenia gravis (MG) in a human."

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

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

D1 Moore (2008) URL:http://elaine-moore.com/LinkClick.aspx?fileticket=fCMSMCpCNzo%3D&tabid=165&mid=603&forcedownload=true

D2 Zhou *et al.* (2007) J. Immunol. 179(12),8562-8567

D4 Anonymous (2007) Safety and Efficacy Study of Eculizumab in Patients With Refractory Generalized Myasthenia Gravis, https://clinicaltrials.gov/archive/NCT00727194/2008_10_07

D5 Tuzun *et al.* (2006) Drug Discovery Today 3(1), 15-20

D7 Alexion Pharmaceuticals, Inc. Press release (23 October 2017)

D11 Würzner and Zimmerhackl (2006) in: *Complement and Kidney Disease*, edited by Peter F. Zipfel, Birkhauser Verlag Basel/Switzerland, pages 149-163

D12 Avant Immunotherapeutics, Inc. Press Release (16 April 2007)

D13 Armstrong (2007) J. Am. Med. Assoc. 297(1),43-51

D14 Mitchell (2007) http://www.upi.com/Health_Business/Analysis/2007/01/02/analysis_alexions_pexelizumab_fails/6113/

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

Inventive step (Article 56 EPC)

Main request and auxiliary request 1 - claim 1

Document D4, disclosing the set-up of a clinical trial study to determine the safety and efficacy of eculizumab in patients with myasthenia gravis (MG), represented the closest prior art.

The proposition of this clinical trial did not provide the skilled person with a reasonable expectation of success that MG could be treated with eculizumab, because targeting the complement system did not

inevitably result in treatment of a complement-associated disorder, as was evident from various unsuccessful attempts to target complement factors in different diseases.

For example, the complement inhibitor sCR-1 (TP-10), which had been considered a suitable drug candidate for the treatment of acute respiratory distress syndrome and acute myocardial infarction, had failed when tested in clinical trials (document D11, page 159, second paragraph). Document D12 confirmed that sCR-1 had indeed been defunded.

Further, as was evident from document D13, the anti-C5 single chain variable fragment pexelizumab did not show any clinical improvement in a phase 3 clinical trial in acute ST-elevation myocardial infarction (page 49, right-hand column, last paragraph), despite the fact that the complement system had been known to be activated in this disease (page 43, left-hand column, last paragraph), inhibition of C5 had been considered "*an attractive target*" (page 43, right-hand column, last sentence), and pexelizumab had resulted in reduced infarct size in experimental models (page 44, left-hand column, first paragraph). These observations were confirmed in document D14.

That the clinical trial protocol disclosed in document D4 did not lead to a reasonable expectation of the skilled person that MG could be treated successfully with an anti-C5 antibody was further underlined by the fact that MG was particularly difficult to treat in humans, as evident from document D7 which disclosed that no therapy for generalised MG had been approved in more than 60 years.

The facts underlying the present case were different from those underlying decisions T 239/16 (point 6.5 of the Reasons) and T 2506/12 (points 3.10 and 3.15 of the Reasons) cited by the examining division. In those cases, contrary to the case in hand, the treatment of the respective diseases with either a similar group of agents or separate agents of the claimed combination was known to the skilled person.

Document D2 did not provide an expectation of success that MG could be treated with an anti-C5 antibody either, because it disclosed the use of a passive immunisation model for MG (passive EAMG), i.e. a model which, according to document D5, was not a suitable model for human MG, as it represented only the effector stage of the disease (page 16, right-hand column, second paragraph).

Consequently, the claimed invention was not obvious to the skilled person and therefore involved an inventive step (Article 56 EPC).

Auxiliary requests 2 and 3

The appellant did not submit any tailor-made arguments for this claimed invention in the context of inventive step.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims of the main request submitted with the statement of grounds of appeal or, alternatively, on the basis of the set of claims of one of auxiliary requests 1 to 3 submitted with the letter of 13 April 2021.

Reasons for the Decision

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

Inventive step (Article 56 EPC)

Main request and auxiliary request 1 - claim 1

Closest prior art and objective technical problem

2. Claimed is an inhibitor of human complement component C5 for use in treating MG in a human, wherein the inhibitor is an anti-C5 antibody (see section V.). One example of such compounds is eculizumab (see application page 8, line 11).

3. The examining division considered that the protocol of a safety and efficacy clinical trial of eculizumab in patients with refractory generalised MG disclosed in document D4 represented the closest prior art, and formulated the objective technical problem as "*the provision of evidence-based medical application of an anti-C5 antibody in human* [*sic*]".

4. According to established jurisprudence of the boards of appeal, the closest prior art should be a teaching directed to the same purpose or effect as the claimed invention (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, I.D.3.2.). The board therefore holds that actual therapies for treatment of MG in humans, such as therapies with immunosuppressants including prednisone, methotrexate, cyclosporine and cyclophosphamide, also disclosed in document D4 (page 1), represent the closest prior art,

rather than the clinical trial protocol which is also disclosed there.

5. The claimed subject-matter differs from the known MG therapies in humans in that the therapeutic is an inhibitor of human complement component C5, wherein the inhibitor is an anti-C5 antibody ("C5 antibody").

6. The application does not attribute a particular technical effect to the claimed therapeutic in the claimed use, which goes beyond the technical effect of the known MG therapies. The objective technical problem can thus be formulated as the provision of an alternative treatment of MG in humans. This has not been contested by the appellant.

Obviousness

7. Document D4 discloses a protocol of a safety and efficacy clinical trial of eculizumab in patients with refractory generalised MG. The results of this clinical trial are not disclosed. Thus, document D4 proposes the antibody eculizumab (an inhibitory C5 antibody) as an alternative therapeutic for refractory generalised MG in humans.

8. Clinical trials are conventionally based on earlier preclinical studies, and the potential therapeutics tested in clinical trials are duly selected based on experimental data suggesting their success (see e.g. decision T 239/16, point 6.5 of the Reasons).

9. Thus, the board considers that the announcement of a detailed safety and efficacy clinical trial protocol for a particular therapeutic and disease provided the skilled person with a reasonable expectation of the

success of this particular therapeutic, unless there was evidence to the contrary in the state of the art. In the case in hand, the board holds that no such evidence to the contrary has been brought forward by the appellant.

10. The appellant has submitted that the disclosure of the clinical trial protocol of document D4 constituted, at most, an invitation for the skilled person to try the treatment of MG with eculizumab. Indeed, MG was particularly difficult to treat in humans, as was evident from document D7 which disclosed that no therapy for generalised MG had been approved in more than 60 years.

11. The board however fails to see how the mere fact that no MG therapy has been approved for a long time would have diminished the expectation of success for the specific clinical trial disclosed in document D4.

12. The appellant further submitted that many clinical trials directed at treating a complement-associated disorder with a complement inhibitor had failed, as evident from the disclosures in documents D11 and D13.

13. The studies disclosed in documents D11 and D13 concern complement inhibitors other than eculizumab (sCR-1 and pexelizumab) to treat diseases different from MG (acute respiratory distress syndrome and acute myocardial infarction). Furthermore, the complement cascade is a complex system involving multiple proteins having been implicated in a large number of different diseases. In view of this complexity, the board is satisfied that the failure of other complement inhibitors to treat diseases unrelated to MG did not necessarily call into question the skilled person's expectation that MG could

be treated successfully with eculizumab. In fact, in the board's view, only evidence relating to the same compound and disease would be suitable for this purpose.

14. Consequently, the board concludes that the disclosure of documents D11 and D13 did not call into question the expectation of success the skilled person had from document D4 announcing a phase 2 clinical trial for the treatment of MG with eculizumab.

15. The appellant further submitted that the teaching in document D2 did "*not support*" the skilled person's expectation of successful treatment of MG in humans with eculizumab, since the experimental animal model used in document D2 was not a suitable model for human MG, as it represented only the effector stage of the disease (see document D5, page 16, right-hand column, first full paragraph).

16. The board considers that the disclosure of the clinical trial in document D4 as such provided the skilled person setting out to provide an alternative therapeutic for the treatment of MG with a reasonable expectation that the treatment of MG in humans with eculizumab would be successful (see point 9.).

17. Furthermore, the teaching of document D2 does not call into question this expectation. In fact, it discloses successful treatment of experimental MG induced in mice with an anti-C5 antibody, which in 2008, i.e. after publication of document D5's review on MG animal models, was considered "*so encouraging that human clinical trials using eculizumab are expected to begin within the next year*" (document D1, second last paragraph on page 2). The skilled person would thus

have considered, even after the publication of document D5, that the animal model used in document D2 was a suitable animal model for human MG and that the successful treatment of experimental MG induced in mice with an anti-C5 antibody would be encouraging for treating MG in humans.

18. Thus, the board concludes that no evidence is on file calling into question that MG could be treated with eculizumab in humans, as proposed in the phase 2 clinical trial study disclosed in document D4.

19. In view of the above considerations, the board holds that the subject-matter of claim 1 of the main request was obvious to the skilled person. Consequently, the subject-matter of claim 1 of the main request and claim 1 of auxiliary request 1 does not involve an inventive step within the meaning of Article 56 EPC.

Auxiliary requests 2 and 3

20. The subject-matter of claim 1 of each of auxiliary requests 2 and 3 differs from the subject-matter of claim 1 of the main request in that the anti-C5 antibody is now explicitly defined as being eculizumab (see section V.).

21. The appellant did not submit any tailor-made arguments for this claimed invention in the context of inventive step.

22. The board considers that the teaching of document D4 provided a reasonable expectation of success for the treatment of MG with the specific anti-C5 antibody eculizumab (see point 16.). The same considerations as for claim 1 of the main request and auxiliary request 1

hence apply to claim 1 of each of auxiliary requests 2 and 3.

23. Consequently, the board holds that the subject-matter of claim 1 of each of auxiliary requests 2 and 3 does not involve an inventive step within the meaning of Article 56 EPC, either.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

B. ter Heijden B. Claes

Decision electronically authenticated