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Datasheet for the decision of 15 March 2021

Case Number: T 2214/17 - 3.3.04

Application Number: 14185297.0

Publication Number: 2975058

IPC: C07K16/40

Language of the proceedings: EN

Title of invention:

Antibodies for use in treating conditions related to specific PCSK9 variants in specific patient populations

Applicant:

Kymab Limited

Headword:

PCSK9 E670G mutants/KYMAB

Relevant legal provisions:

EPC Art. 56
RPBA Art. 12(4)
RPBA 2020 Art. 13(1)

Keyword:

Late-filed request - admitted (yes)
Amendment to appeal case - suitability of amendment to resolve issues raised (yes)
Inventive step - obvious alternative

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2214/17 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 15 March 2021

Appellant: (Applicant)	Kymab Limited The Bennet Building (B930) Babraham Research Campus Cambridge CB22 3AT (GB)
Representative:	CMS Cameron McKenna Nabarro Olswang LLP Cannon Place 78 Cannon Street London EC4N 6AF (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 24 April 2017 refusing European patent application No. 14185297.0 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Chakravarty
Members:	O. Lechner
	L. Bühler

Summary of Facts and Submissions

I. The applicant (appellant) filed an appeal against the decision of the examining division refusing European patent application EP 14 185 297.0 ("the application") entitled "*Antibodies for use in treating conditions related to specific PCSK9 variants in specific patient populations*".

II. In the decision under appeal, the examining division held that the set of claims before it did not involve an inventive step (Article 56 EPC).

III. With the statement of grounds of appeal, the appellant filed a set of claims as a main request, as well as sets of claims of auxiliary requests 1 to 4, all of which were filed for the first time on appeal. They also filed seven documents, of which three are referred to in this decision (see documents A14, A15 and A18 below). The remaining four documents are not relevant to this decision.

IV. The board issued summons to oral proceedings, as well as a communication pursuant to Article 15(1) RPBA, setting out the board's preliminary opinion on the issues in the appeal. In this communication, the board cited documents A22 and A23, see below.

V. In a letter dated 5 February 2021, the appellant requested that the oral proceedings be conducted by videoconference.

VI. In a further letter, the appellant filed a set of claims of a new main request and withdrew the sets of claims of the previous main request and of auxiliary

requests 1 to 4. They also filed three further documents (A24 to A26, see below) and withdrew their request to admit documents A16, A17, A20 and A21.

VII. Oral proceedings before the board took place by videoconference, as requested by the appellant. At the end of the oral proceedings, the Chair announced the board's decision.

VIII. Claim 1 of the main request reads as follows:

"1. An antibody or antibody fragment for use in a method of reducing cholesterol level or maintaining previously reduced cholesterol level in a human in need thereof, wherein the antibody is evolocumab and said human comprises (i) an IGHG2*01 human heavy chain constant region gene segment and (ii) a nucleotide sequence encoding proprotein convertase subtilisin/ kexin type 9 (PCSK9) that comprises a C-terminal domain comprising a mutation E670G in SEQ ID NO: 1."

IX. The following documents are referred to in this decision

A14: US2012/0093818A1

A15: Poirier et al., The biology of PCSK9 from the *endoplasmic reticulum to lysosomes: new and emerging therapeutics to control low-density* lipoprotein cholesterol; Drug Design, Development and Therapy (2017), volume 7, pages 1135-1148

A18: Awan et al; Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9): Lessons Learned from Patients with Hypercholesterolemia; Clinical Chemistry (2014), volume 60, issue 11, pages 1380-1389

A22: Jefferis et al.; Human immunoglobulin allotypes; MAbs (2009), volume 1, issue 4, pages 332-338

A23: Cariou et al.; Clinical aspects of PCSK9; Atherosclerosis (2011), volume 216, pages 258–265

A24: Chen et al.; A Common PCSK9 Haplotype, Encompassing the E670G Coding Single Nucleotide Polymorphism, Is a Novel Genetic Marker for Plasma Low-Density Lipoprotein Cholesterol Levels and Severity of Coronary Atherosclerosis; Journal of the American College of Cardiology (2005), volume 45(10), pages 1611-1619

A25: Cameron et al.; Mutation S462P in the PCSK9 gene reduces secretion of mutant PCSK9 without affecting the autocatalytic cleavage; Atherosclerosis (2009), volume 203, pages 161–165

X. The arguments of appellant relevant to the present decision are summarised as follows:

Admittance of the main request (Article 13(1) RPBA)

The main request was filed in direct response to objections raised by the board in its communication pursuant to Article 15(1) RPBA under Article 123(2) and 84 EPC. The amendments were not complex and directly addressed the objections and thus were admissible.

Main request - claim 1

Inventive step (Article 56 EPC)

Closest prior art and difference

Document A14 represented the closest prior art and differed from the subject-matter of claim 1 in that the patient to be treated expresses

(i) the PCSK9 E670G variant, and

(ii) the IGHG2*01 allele.

Technical effect and problem to be solved

The application showed for the first time that evolocumab could bind to the clinically-relevant PCSK9 E670G mutant with a similar affinity as to the most common form of PCSK9 (reference was made to variants "PCSK9 a" (most common form), "PCSK9 c" (670G mutant) and "PCSK9 r" (474V and 670G double mutant) in Table 3 of the application). As discussed in paragraphs [0624] to [0628] of the published application, matching the administered antibody's constant region allotype to the patient's genotype, meant that the antibody was compatible with the patient and reduced the risk of an anti-antibody immune response.

The problem to be solved was how to improve cholesterol lowering treatment in humans using a PCSK9 inhibitor.

Obviousness

There was no suggestion in the closest prior art represented by document A14, of tailoring treatment to particular PCSK9 variants. Based on the disclosure of document A14, a skilled person would not have had a

reasonable expectation that an antibody comprising the variable domains of evolocumab would bind PCSK9 variants containing the natural E670G mutation with therapeutic amenable affinity. The E670G mutation was located in the cysteine-rich C-terminal domain of PCSK9 (see document A24, page 1617, right column, lines 13 to 14).

It had been expected that anti-PCSK9 antibodies did not bind all PCSK9 forms equally well, as evident, e.g., from document A14, in which 86 of the antibodies selected for binding to wild-type PCSK9 did not bind the D374Y mutant (see paragraph [0445]). Paragraph [0622] of document A14 also described that it was not possible to predict which mutations in PCSK9 would be expected to have an impact on binding of a particular antibody.

Document A15 described that a mutation in the C-terminal domain (C679X) led to a loss of function of PCSK9 and a lowering of circulating LDL-C (see Figure 1 and page 1136, left column, first paragraph).

Document A18 also described a number of mutations in the C-terminal domain that led to a loss-of-function or gain-of-function of PCSK9 (see Figure 1C, right-hand side, which listed 10 gain-of-function mutations in the C-terminal domain and 7 loss-of-function mutations in the same region). Page 1382 of document A18, fifth last sentence also described that the C-terminal domain mutation C679X was a loss-of-function mutation associated with a decreased in LDL-C and a reduction in atherosclerotic disease of 88%.
Document A25 described that it was assumed that the C679X mutant form of PCSK9 was retained in the

endoplasmic reticulum due to abnormal folding (see page 164, right-hand column, first paragraph).

Thus, a skilled person would have been aware that the C-terminal domain played a significant role in the regulation of PCSK9 function, despite not being the site of direct binding of PCSK9 to LDLR.

Based on the observations made in the above mentioned documents, a skilled person would have expected that the E670G variant would significantly influence the binding of evolocumab to its target, and therefore would not have expected that the antibody could be successfully used in the treatment of patients carrying the PCSK9 E670G variant.

The invention also lay in the realisation of immunogenicity (i.e., anti-drug antibodies) against evolocumab in humans with elevated cholesterol that hampered utility as a medicament. The invention selected for patients whose genomic variation (in the antibody constant region genes) matched the administered antibody, wherein the genomic constant gene variation was naturally found together with PCSK9 variation in humans that correlated with elevated cholesterol. In this case, the E670G variation correlated with elevated cholesterol and coronary atherosclerosis in humans (see document A24) such variation was found in humans carrying the IGHG2*01 allotype. Thus, the problem was also solved in an inventive way by selecting a human patient whose genomic profile was one where the patient expresses E670G PCSK9 and also where the patient expresses IGHG2*01-type antibodies, and thus matching the administered antibody that was efficacious for treating elevated cholesterol by specifically binding to PCSK9

E670G that correlated with elevated cholesterol and the IGHG2*01 allotype.

XI. The appellant's requests at the end of the oral proceedings were:

- that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed by letter dated 22 February 2021, and
- that documents A14, A15, A18, A24, and A25 be admitted into the proceeding.

Reasons for the Decision

Admissibility of the appeal

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

Admittance of the main request (Article 13(1) RPBA)

2. The board decided to admit the new main request into the appeal proceedings.

Admittance of documents A14, A15, A18, A24, and A25

3. The board decided to admit documents A14, A15, A18, A24 and A25 into the proceedings (Article 12(4) RPBA 2007). The board did not decide on the admission of the other documents submitted during the appeal proceedings as they were not relevant to the decision.

Main request - claim 1

The claimed invention

4. Claim 1 is drafted as a second medical use claim pursuant to Article 54(5) EPC. The substance used is a monoclonal antibody (evolocumab) that binds to proprotein convertase subtilisin/kexin type 9 (PCSK9; see SeqID 1). The therapeutic effect is reducing or maintaining previously reduced cholesterol levels in a subpopulation of humans characterized by i) being carriers of a PCSK9 variant comprising the E670G mutation in its C-terminal domain and ii) expressing an IGHG2*01 human heavy chain constant region gene segment. Attaining the claimed therapeutic effect is a functional technical feature of the claim.

Inventive step (Article 56 EPC)

Closest prior art

5. The board, in agreement with the appellant, considers that document A14 can represent the closest prior art for the assessment of inventive step of the claimed invention.

6. Document A14 discloses the anti-PSCK9 antibodies 21B12 and AMG145 (= evolocumab). Antibody 21B12 has the identical CDRs (see Seq 49 and 23, respectively) as evolocumab, the VH and VL sequences differing only by replacement of the N-terminal Q by E. Figure 27A of document A14 depicts the 21B12 epitope "hits" as mapped onto a crystal structure of PCSK9 with the 21B12 antibody. Example 30 (and esp. paragraph [0538]) identifies the core residues of the interaction of antibody 21B12 with PCSK9 as being S153, S188, I189, Q190, S191, D192,

R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, and F379. Document A14 also addresses the use of fully human anti-PCSK9 antibodies to avoid rapid clearance of the antibodies and/or the generation of an immune response against the antibody in the patient (see e.g. [0288] to [0291]). Antibody AMG145 and the information on its affinity for PCSK9 at different pH values are provided in Tab 45.3 on page 70. The anti-PCSK9 antibodies disclosed are described as being useful for preventing or treating PCSK9-mediated diseases such as hypercholesterinaemia, atherosclerosis, or cardiovascular diseases (see paragraphs [0030], [0376]. Paragraph [0279] mentions that the disclosed antibodies ("antigen binding proteins") bind to PCSK9 variants such as variants at position 474, E620G and/or E670G..."*Given the cross-reactivity data presented herein, it is believed that the present antibodies will readily bind to the above variants*."

7. The subject-matter of claim 1 differs from the above mentioned closest prior art in that, in the former the patients to be treated are restricted to those in a subgroup having:

(i) the PCSK9 E670G variant, and

(ii) the IGHG2*01 allele,

This was not disputed by the appellant.

Technical effect and objective technical problem

8. The technical effect of the first difference (i), is the treatment of patients carrying the E670G PCSK9 variant with evolocumab in order to reduce cholesterol levels or to maintain previously reduced cholesterol levels.

The effect of the second difference (ii), is that potential problems associated with a mismatch between the IGHG2 allotype and that of evolocumab are avoided.

9. The board notes that the application contains no evidence demonstrating that the distinguishing features (i) and (ii) result in an improved treatment of PCSK9 related conditions as compared to the larger patient group treated in document A14, as was alleged by the appellant. Nor has any evidence to this effect been provided by the appellant. Therefore, an improved treatment of PCSK9 related conditions cannot be taken into account by the board as a technical effect of the claimed invention or in establishing the technical problem to be solved.

10. The objective technical problem is thus the provision of an antibody therapy suitable for reducing cholesterol levels or maintaining previously reduced cholesterol levels in a new subgroup of patients and avoidance of potential problems caused by a mismatch between the IGHG2 allotype of the patient and that of evolocumab.

Obviousness

Feature (i) treatment of patients comprising the E670G PCSK9 variant

11. The skilled person, starting from the use of the anti-PCSK9 antibody AMG1345/evolocumab to attenuate or inhibit a PCSK9-mediated disease or condition, such as hypercholesterolemia, hyperlipidemia, as disclosed in the closest prior art document A14 and seeking a solution to the above problem, knew that anti-PCSK9 antibodies binding to the catalytic domain of the

protein could be used to prevent or treat PCSK9-mediated diseases.

12. The appellant argued that the skilled person would not have expected that treatment with evolocumab would be effective in patients carrying the PCSK9 E670G variant, in view of the fact that other PCSK9 variants showed abnormal folding, retention in the endoplasmic reticulum and/or loss of function, as disclosed e.g. in documents A18 and A25. Mutations impacting the antibody's binding site on the target would likely impact the antibody's binding ability. Thus, there was no reasonable expectation that any residue in the PCSK9 molecule, including those of known variants, could be mutated and that evolocumab could still bind the target, let alone with therapeutically-useful and high affinity as demonstrated in the application.

13. However, this argument is not convincing because the skilled person knew that the PSCK9 variants mentioned in documents A18 and A25 (mutations of the C679 or the S462 positions, respectively) had an impact on the structure and consequently also activity of PCSK9, whereas this was not the case for position E670. Indeed, the E670G variant was known to be physiologically active (see review article A23, page 260, left-hand column, paragraph 1, reference 44 corresponds to document A24 in these proceedings).

14. Knowing that the PCSK9 E670G variant is physiologically active, the skilled person would not have expected that the mutation in position 670 would significantly affect the binding of an antibody targeting the catalytic domain of PCSK9. This view is supported by 3D structure of PCSK9 as provided e.g. in Figure 1 of the application or Figure 2 and 4A of document A15 and the

epitope reported for evolocumab, both of which were known to the skilled person (see Reasons point 6. above).
Finally, the closest prior art already explicitly mentions in paragraph [0279] that the disclosed antibodies ("antigen binding proteins") are expected to bind to the PCSK9 variant E670G. There is also no evidence in the application of a difference in the effect of treating the sub-group of patients defined in the claim compared with the group of patients treated in document A14.

15. A skilled person would therefore have considered it obvious to use evolocumab to treat patients carrying the E670G PCSK9 variant.

16. It is the board's view that, based on the teaching in the closest prior art document A14, together with the common general knowledge that the PCSK9 E670G variant is functional (see e.g. review article A23, the skilled person would have had no doubts as to the efficacy of evolocumab in patients carrying the E670G PCSK9 mutation. The selection of this patient-subgroup is not associated with any technical effect. A selection which is not associated with a technical effect is often described as "arbitrary" in the jurisprudence (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, I.D.9.10 and 9.19.8). Such an arbitrary selection, by the very fact of it being arbitrary, does not involve an inventive step (*ibid*).

*Feature (ii) treatment of patients comprising the IGHG1*01 allele*

17. The board considers that, faced with the problem of avoiding potential problems due to anti-antibody

allotype reactions, the skilled person would have used evolocumab only in the corresponding population of IGHG2*01-positive patients and/or used antibodies with a matched allotype, i.e. in case of IGHG2*01 the "*G2m..*" (or G2m23 negative) allotype.

18. This is because the potential immunogenicity of heterozygous allotypic antibodies was common general knowledge in the art. For example, document A22, reports that immunoglobulin allotypes are a potential source of therapeutic antibodies' immunogenicity and that the development of two or more allotypic variants is necessary in case anti-allotype responses arise (see page 333 as well as the conclusions on page 337).

19. In view of the above considerations, the subject-matter of claim 1 lacks an inventive step.

20. The sole claim request is not allowable.

Order

For these reasons it is decided that:

- The appeal is dismissed.

The Registrar: The Chairman:

A. Chavinier-Tomsic A. Chakravarty

Decision electronically authenticated