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Datasheet for the decision of 15 March 2021

Case Number: T 2044/17 - 3.3.04

Application Number: 14199053.1

Publication Number: 2975059

IPC: C07K16/40

Language of the proceedings: EN

Title of invention:
Antibodies for use in treating conditions related to specific PCSK9 variants in specific patients 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

Boards of Appeal

Chambres de recours

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Case Number: T 2044/17 - 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 application No. 14199053.1 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 14 199 053.1 ("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 5, 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 A15, A18 and A19 below). The remaining four documents are not relevant to this decision.

IV. The board issued a 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 5. They also filed three further documents (A24 to A26, see below).

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 alirocumab and said human comprises an IGHG1*01 human heavy chain constant region gene segment and 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

D13: WO 2010/077854 A1

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

A19: Gouni-Berthold; Systematic review of published Phase 3 data on anti-PCSK*9* monoclonal antibodies in patients with hypercholesterolaemia; British Journal of Clinical Pharmacology (2016), volume 82, pages 1412-1443

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

A26: Online Supplementary Data for document A25, 3 Figures

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 D13 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 IGHG1*01 allele.

Technical effect

The application showed for the first time that alirocumab 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.

Technical problem

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

Obviousness

There was no suggestion in the closest prior art represented by document D13, of tailoring treatment to particular PCSK9 forms. Example 16 in document D13 demonstrated that the affinity of the 316P antibody varied depending on the PCSK9 mutant tested. Paragraph [0165] actually reported reduced binding to PCSK9 variants with mutations in positions D238, S153, E159 or D343.
A skilled person would not have had a reasonable expectation that alirocumab could bind PCSK9 forms containing the natural E670G mutation with a therapeutically amenable affinity. There was no motivation to look for this particular mutant amongst the about 160 known PCKS9 variants. The E670G mutation could have influenced the catalytic domain's structure and consequently disrupted the alirocumab binding site even if the mutation was located in the C-terminal region of PCSK9.

Document A24 taught that the E670G variant was an important determinant of plasma levels of low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) and was associated with the severity of coronary atherosclerosis in the Lipoprotein Coronary Atherosclerosis Study (LCAS) population.

Document A18 showed in Figure 1 that there were both gain of function and also loss of function PCSK9 variants based on mutations in the C-terminal domain.

Document A25, page 164, right-hand column, paragraph 1, indicated that PCSK9 variants S462P, G236S and C679X were associated with abnormal folding and retention of the mutant protein in the endoplasmic reticulum (ER).

The last paragraph of the Discussion in document A25, highlighted that the absolutely conserved S462 position in PCSK9 was important for normal folding of the molecule. Mutation of this position, which was located in the C-terminal domain, resulted in a loss of function of this PCSK9 variant.

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 alirocumab 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.

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 to A20, A24, and A25 be admitted into the proceedings.

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 A15, A18, A19 and A24 to A26

3. The board decided to admit documents A15, A18 and A19 and A24 to A26 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 (alirocumab) that binds to proprotein convertase subtilisin/kexin type 9 (PCSK9; see SEQ ID 1). The therapeutic effect is reducing or maintaining previously reduced cholesterol levels in a sub-population of humans characterised by i) being carriers of a PCSK9 variant comprising the E670G mutation in its C-terminal domain and ii) expressing an IGHG1*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. Document D13 was considered as the closest prior art both in the decision under appeal and by the appellant. The board sees no reason to differ.

6. Document D13 discloses the anti-PCSK9 antibody "316P" which is an alternative designation for alirocumab. The antibody is described as being useful for preventing or treating PCSK9-mediated diseases such as hypercholesterinaemia, atherosclerosis, or cardiovascular diseases (see paragraphs [0035] to [0039]). Fig 14 discloses the *in vivo* effects of antibody 316P on serum LDL-C levels. Document D13 does not mention the E670G variant or the immunoglobulin heavy chain constant region gene segment allele of the antibodies used.

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 IGHG1*01 allele,

This was not disputed by the appellant.

8. The technical effect of the first difference (i), is the treatment of patients carrying the PCSK9 E670G variant with alirocumab 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 IHHG1 type and that of alirocumab 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 D13, 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 IGHG1 type of the patient and that of alirocumab.

Obviousness

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

11. The skilled person, starting from the use of the anti-PCSK9 antibody 316P to attenuate or inhibit a PCSK9-mediated disease or condition, such as hypercholesterolemia, hyperlipidemia, as disclosed in the closest prior art document D13 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. It was also part of the skilled person's common general knowledge that the PCSK9 E670G variant is physiologically active and that its presence in a

patient was a predictor of large vessel atherosclerosis stroke (see review article A23, page 260, left-hand column, paragraph 1, reference 44 corresponds to document A24 in these proceedings).

13. Example 16 of the application (see Table 27 on pages 45 to 46) discloses that antibody 316P (= alirocumab) showed decreased affinity for PCSK9 variants carrying mutated amino acids within their prodomain (amino acids 1 to 152) or the catalytic domain (amino acids 153 to 425) compared to wild-type PCSK9. Variants with mutations in the C-terminal domain (amino acids 426 to 692) were not tested. The crucial amino acids for the binding of antibody 316P to PCSK9 are within the catalytic domain, specifically at positions 153, 159, 238, and 343 (see paragraph [0165] of document D13).

14. Knowing that the PCSK9 E670G variant is physiologically active, the skilled person would have expected that the mutation in position 670 would not significantly affect the binding of an antibody targeting the catalytic domain of PCSK9. This expectation was supported by the known 3D structure of PCSK9 as provided e.g. in Figure 1 of the application or Figure 2 and 4A of document A15 from which it was apparent that the C-terminal domain of PCSK9 (in which the E670G mutation resides) is spatially opposed to the catalytic, LDLR-binding site to which alirocumab binds (see document D13, paragraph [0165] on page 46). Therefore, a skilled person would have considered it obvious to use alirocumab for treating these patients.

15. There is 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 D13.

16. The appellant argued that the skilled person would not have expected that treatment with alirocumab 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 alirocumab could still bind the target, let alone with therapeutically-useful and high affinity as demonstrated in the application.

17. 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 position, 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 know to be physiologically active (see document A23, page 260, left-hand column, paragraph 1)

18. It is the board's view that, based on this knowledge, the skilled person would have no doubts as to the efficacy of alirocumab in patients carrying the PCSK9 E670G mutation. Thus, 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*

19. The board considers that faced with the problem of avoiding potential problems due to anti-antibody allotype reactions, the skilled person would have used alirocumab only in the corresponding population of IGHG1*01-positive patients and/or used antibodies with a matched allotype, i.e. in case of IGHG1*01 the G1m17,1 allotype.

20. 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).

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

22. 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