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Datasheet for the decision of 9 January 2023

Case Number: T 3165/19 - 3.3.08

Application Number: 15712241.7

Publication Number: 3119810

IPC: C07K16/40, A61K39/395, A61P9/00

Language of the proceedings: EN

Title of invention:
Methods for reducing cardiovascular risk

Applicants:
Sanofi Biotechnology
Regeneron Pharmaceuticals, Inc.

Headword:
PCSK9 antibody for reducing cardiovascular risk/SANOFI

Relevant legal provisions:
EPC Art. 56, 111(1)
RPBA 2020 Art. 11, 13(2)

Keyword:
Inventive step - reasonable expectation of success (no)
Amendment after summons - change of case (no)
Remittal - special reasons for remittal (yes)

Decisions cited:
T 0239/16

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Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 3165/19 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 9 January 2023

Appellant: (Applicant 1)	Sanofi Biotechnology 54 rue La Boétie 75008 Paris (FR)
Appellant: (Applicant 2)	Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591 (US)
Representative:	Zwicker, Jörk ZSP Patentanwälte PartG mbB Hansastraße 32 80686 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 18 June 2019 refusing European patent application No. 15712241.7 pursuant to Article 97(2) EPC**

Composition of the Board:

Chair	B. Claes
Members:	A. Schmitt
	P. de Heij

Summary of Facts and Submissions

I. The applicants' ("appellants'") appeal lies from the decision of the examining division refusing European patent application No. 15 712 241.7, which had been filed as an international patent application published as WO 2015/142668 ("application"). The title of the application is "*Methods for reducing cardiovascular risk*".

II. The examining division considered sets of claims of a main request and six auxiliary requests. With respect to the set of claims of auxiliary request 1, the examining division took a reasoned decision only on inventive step. It considered that the subject-matter of claim 1 of auxiliary request 1 did not involve an inventive step (Article 56 EPC) starting from document D4 or, alternatively, document D15 as closest prior art, and *inter alia* taking into account document D7, which showed that elevated levels of LDL-C were commonly associated with cardiovascular risk.

Claim 1 of this auxiliary request 1 read as follows:

"1. An antibody or an antigen-binding fragment thereof that specifically binds and inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) for use in a method for reducing cardiovascular risk in a high cardiovascular risk patient following an acute coronary syndrome (ACS), wherein said patient has hypercholesterolemia and exhibits inadequate control of other atherogenic lipoproteins despite treatment with a maximum tolerated daily dose statin therapy, wherein the antibody or the antigen-binding fragment thereof has heavy and light chain CDR amino acid

sequences having SEQ ID NOs: 2 (HCDR1), 3 (HCDR2), 4 (HCDR3), 7 (LCDR1), 8 (LCDR2) and 10 (LCDR3), and wherein the use comprises administering the antibody or antigen-binding fragment thereof to the patient at a dose of 75 mg or 150 mg."

III. With the statement of grounds of appeal, the appellants submitted sets of claims of a main request and auxiliary requests 1, 2 and 3 and two documents. The set of claims of auxiliary request 1 was identical to the set of claims of auxiliary request 1 considered by the examining division (see section II.).

IV. The board summoned the appellants to oral proceedings as they had requested, and issued a communication pursuant to Article 15(1) RPBA, in which it, *inter alia*, expressed the preliminary view that the subject-matter of claim 1 of auxiliary request 1 involved an inventive step.

V. In the response to the board's communication dated 15 July 2022, the appellants submitted a set of claims of a new main request and maintained auxiliary requests 1, 2 and 3 filed with the statement of grounds of appeal.

The new main request differs from auxiliary request 1 submitted with the statement of grounds of appeal only in that in claim 1 (see sections II. and III.) the expression "acute coronary syndrome (ACS)" has been replaced by the expression "acute coronary syndrome (ACS) event".

VI. The board cancelled the oral proceedings.

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

D4 E. A. Stein et al., Current Atheroscleosis Reports 15(3), 2013, 1-14

D7 C. R. Rahilly-Tierney et al., Preventive Cardiology 12(2),2009, 80-87

D10 A. Liakis et al., Systematic review protocol, 2016, Version: 1.32/06.01.2014 Final, 1-16

D11 R. DuBroff and M. de Lorgeril, World J. Cardiol. 7(7), 2015, 404-409

D12 U. Landmesser, European Heart Journal 34, 2013, 1254-1257

D13 J. H. Tanne, BMJ 333, 2006, 1237

D14 A. M. Lincoff et al., N. Engl. J. Med. 376, 2017, 1933-1942

D15 A. Rossebø et al., N. Engl. J. Med. 359, 2008, 1343-1356

D17 E.-Y. Lee and K.-H. Yoon, J. Lipid. Atheroscler. 7(l), 2018, 1-11

VIII. The appellants' arguments relevant to the decision are summarised as follows.

Main request
Admittance (Article 13(2) RPBA)

Paragraphs [0007], [0012] and [0105] of the application formed the basis for the amendment.

Inventive step (Article 56 EPC) - claim 1

Document D4 described an ongoing phase 3 clinical trial to evaluate the effect of the antibody alirocumab on the occurrence of cardiovascular events in high cardiovascular risk patients who had experienced an acute coronary syndrome (ACS) event and were not adequately controlled with statin therapy. Document D4 did however not disclose the results of this clinical trial and did therefore not contain an enabling disclosure for this treatment. Hence document D4 was not comprised within the state of the art and its disclosure could therefore not represent the closest prior art in the assessment of inventive step.

In any event, it was not the disclosure in document D4 but the disclosure in document D15 which represented the closest prior art. The latter was directed to the same purpose, the reduction of cardiovascular risk, here by treating high cardiovascular risk patients with a combination of simvastatin and ezetimibe. The technical effect of the difference of the claimed subject-matter from document D15's teaching (an inhibitory proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody instead of ezetimibe for use in the treatment) was that the reduction of cardiovascular risk, in particular all-cause mortality, was improved.

This was evident from post-published document D17, which could be taken into account to demonstrate the technical effect because all-cause mortality was related to the technical problem formulated in the application.

The objective technical problem was therefore the provision of an improved treatment for the reduction of cardiovascular risk, specifically one that reduced all-cause mortality. The claimed solution was not obvious to the skilled person because neither a direct link between PCSK9 inhibition and reduced cardiovascular risk nor a clear link between reduced low-density lipoprotein-cholesterol (LDL-C) levels and cardiovascular risk had been established in the art. It was known that treatment with statins lowered LDL-C levels and reduced cardiovascular risk (see e.g. document D7). However, not all drugs known to lower LDL-C levels necessarily reduced cardiovascular risk, as was evident from documents D10 to D14. Moreover, effects of PCSK9 loss-of-function mutations on a subject's cardiovascular risk, as summarised in document D4, could not establish this link either, since loss-of-function mutations had cellular effects different from those achieved by an inhibitory PCSK9 antibody.

Consequently, neither the teaching in document D7 on the effects of statins on cardiovascular risk nor the teaching in document D4 on the association of PCSK9 loss-of-function mutations with reduced cardiovascular risk could lead the skilled person reasonably to expect that alirocumab treatment would reduce cardiovascular risk in the patient group recited in the claim. Since several putative alternative LDL-C-lowering agents were known in the art, the selection of alirocumab as

therapeutic agent for the treatment recited in the claim involved an inventive step.

If nevertheless document D4 was used as the starting point for assessing inventive step, then the objective technical problem had to be defined as the provision of a further medical use for alirocumab. For the same reasons as when starting from the disclosure in document D15, the claimed solution was not obvious to the skilled person in the absence of a link between PCSK9 inhibition and reduced cardiovascular risk and between reduced LDL-C levels and cardiovascular risk.

IX. As the board understands, the appellants requested that the decision under appeal be set aside, that the main request be admitted into the appeal proceedings and that the case be remitted to the examining division for further prosecution.

Reasons for the Decision

1. The appeal is admissible.

Main request

Admittance (Article 13(2) RPBA 2020)

2. Under Article 13(2) RPBA 2020, in cases where a communication under Rule 100(2) EPC has not been issued, any amendment to a party's appeal case made after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

3. The only amendment compared with the set of claims of auxiliary request 1 submitted with the statement of grounds of appeal was that the term "event" was introduced in claim 1 in the context of the expression "method for reducing cardiovascular risk in a high cardiovascular risk patient following an acute coronary syndrome (ACS) event".

4. The feature "following an acute coronary syndrome (ACS)" indicates that the patient to be treated has previously experienced an ACS. It has the same technical meaning as "experiencing an ACS *event*". The introduction of the term "event" is therefore a mere clarification. This view is supported by the description of the application, which uses these two terms synonymously, as is evident from for example paragraphs [0003] and [0004] of the application. Paragraph [0003] describes the invention as providing "*methods for reducing cardiovascular risk and lowering atherogenic lipoproteins in high cardiovascular risk patients following acute coronary syndrome*" (see page 1, lines 28 to 30 of the description). A few lines further down on the same page (page 1, lines 32 to 34), paragraph [0004] describes an embodiment of the invention as "*a method for reducing cardiovascular risk in a high cardiovascular risk patient within 12 months following an acute coronary syndrome (ACS) event*".

5. Consequently, the addition of the term "event" to the expression "acute coronary syndrome" does not change the claimed subject-matter and hence does not change the case.

6. In view of the above considerations, the filing of the set of claims of the main request did not amount to an

amendment of the appellants' appeal case. Consequently, the board decided to admit the main claim request into the appeal proceedings.

Inventive step (Article 56 EPC)

Closest prior art

7. The examining division considered that, among the cited documents, the disclosure in document D4 constituted the most suitable starting point for assessing inventive step. Document D4 describes an ongoing phase 3 clinical trial to evaluate the effect of alirocumab (REGN727/SAR236553), an inhibitory anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody comprising the amino acid sequences as defined in claim 1, on the occurrence of cardiovascular events in high cardiovascular risk patients who had experienced an ACS event and were not adequately controlled with statin therapy (see last full sentence on page 10 and last entry in Table 4 of document D4).

8. The appellant argued that since document D4 did not disclose the outcome of this ongoing clinical trial it neither contained an enabling disclosure for this treatment nor was comprised within the state of the art, and could therefore not represent the closest prior art in the assessment of inventive step.

9. The board, however, does not agree that the teaching in document D4 (summarised in point 7. above) could be disregarded. The fact that document D4 does not disclose the outcome of the described ongoing clinical trial has the consequence neither that document D4 does not form part of the state of the art as defined in Article 54(2) EPC for the claimed invention nor that it

should be excluded from the assessment of inventive step by the problem-solution approach. Indeed, the teaching in document D4 that a clinical trial is ongoing, where a particular patient group is treated with alirocumab with the - explicitly disclosed - purpose of identifying whether such a treatment has an effect on these patients' cardiovascular risk, forms part of the state of the art.

10. Moreover, since the teaching in document D4 is concerned with the treatment of the same or a similar patient group with the same therapeutic agent as recited in claim 1, this teaching is technically closely related to the claimed subject-matter, and the skilled person must be assumed to have particular knowledge of document D4's teaching. This disclosure in document D4 therefore represents a suitable starting point for assessing inventive step.

11. The appellants insisted on document D15 representing the closest prior art. Document D15 discloses that treatment of high cardiovascular risk patients suffering from mild to moderate asymptomatic aortic stenosis with a combination of simvastatin and ezetimibe reduces the incidence of ischaemic cardiovascular events. Document D15 is therefore directed to the same purpose as the claimed subject-matter, i.e. the reduction of cardiovascular risk in high cardiovascular risk patients, and is at least a suitable starting point for assessing inventive step of the claimed subject-matter. Whether document D15 is closer to the claimed subject-matter than document D4 is irrelevant, as the claimed subject-matter must involve an inventive step starting from either document. However, document D15 will be assessed first.

Document D15

12. The claimed subject-matter differs from the disclosure in document D15 in that the therapeutic agent is an anti-PCSK9 antibody as defined in the claim, and not ezetimibe. According to the claim, this antibody is for use in a method for reducing cardiovascular risk in a high cardiovascular risk patient who has experienced an ACS event, has hypercholesterolaemia and exhibits inadequate control of other atherogenic lipoproteins despite treatment with a maximum tolerated daily dose statin therapy (hereinafter "high cardiovascular risk patient inadequately controlled by statin therapy").

13. The appellants considered that document D17, which was published after the application's filing date and showed an improvement in all-cause mortality over that disclosed in document D15, must be taken into account in formulating the technical problem. However, in view of the considerations in points 14. to 28. below, it can be left undecided whether the teaching in document D17 could indeed be taken into account for this purpose. Considering only the application's teaching, the objective technical problem is, as correctly considered in the decision under appeal, the provision of an *alternative* agent for use in a method for reducing cardiovascular risk in a high cardiovascular risk patient inadequately controlled by statin therapy.

Obviousness

14. In deciding whether or not the claimed subject-matter was obvious to the skilled person, it must be assessed whether the skilled person would reasonably have expected that treatment of a high cardiovascular risk

patient inadequately controlled by statin therapy with an anti-PCSK9 antibody as defined in the claim would reduce this patient's cardiovascular risk.

15. The examining division considered that the skilled person might reasonably expect that the outcome of the clinical trial disclosed in document D4 would demonstrate that alirocumab reduced cardiovascular risk in high cardiovascular risk patients. Alirocumab was known to reduce the levels of low-density lipoprotein cholesterol (LDL-C) and other atherogenic lipids in patients with or without additional statin treatment, and elevated levels of these lipids were associated with cardiovascular risk. Hence compounds which reduced the levels of these lipids could be expected also to reduce cardiovascular risk, an effect already known for statins. Moreover, loss-of-function mutations in PCSK9 were associated with reduced LDL-C levels and protection from cardiovascular risk, which established a direct link between inhibition of PCSK9 and reduction of cardiovascular risk. The disclosure in *inter alia* documents D10 to D14 concerned compounds which exerted their lipid-lowering effect via mechanisms different from those of PCSK9 inhibitors, and therefore could not reduce the skilled person's expectation that inhibitory PCSK9 antibodies would reduce a patient's cardiovascular risk.

16. The board is however not persuaded by this line of argument. A correlation between the magnitude of (statin)-induced LDL-C reduction and the magnitude of cardiovascular risk reduction has indeed been described in the art (see document D7, in particular Tables I and II). However, the claim relates to the treatment of patients who do not sufficiently respond to statin therapy and therefore exhibit hypercholesterolaemia and

inadequate control of other atherogenic lipoproteins *despite* statin treatment (see sections II. and V.).

17. For this patient group, as demonstrated in documents D12 and D13, no clear link between pharmacologically reduced LDL-C levels and reduced cardiovascular risk exists. Document D12 discloses that when niacin was added to statin treatment the patients' LDL-C levels were further lowered but their cardiovascular risk was not reduced (see document D12, pages 1255-1256 and Figure 2). Document D13 discloses that the drug torcetrapib, when taken in combination with a statin, even had an adverse effect on cardiovascular outcome despite lowered LDL-C levels (see third and fourth column of document D13).

18. The board is not persuaded by the examining division's argument that the teaching in documents D12 and D13 should be disregarded because the compounds assessed in these documents achieved the lowering of the LDL-C levels by a mechanism different from that of an inhibitory PCSK9 antibody. In fact, the outcome of the treatment with the compounds of documents D12 and D13 and the claimed PCSK9 antibody is the same (an LDL-C level lowered beyond the level achieved by statin treatment). If such an LDL-C level which had been lowered further was indeed directly linked to the reduction in the patient's cardiovascular risk, as alleged in the decision under appeal, it would occur irrespective of how the reduction in the LDL-C level was achieved.

19. Consequently, the teaching in documents D12 and D13 demonstrates that no such direct link existed and that the skilled person therefore could not reasonably have expected that the treatment of high cardiovascular risk

patients inadequately controlled by statin therapy with a compound that lowers LDL-C levels in these patients, such as an anti-PCSK9 antibody, would necessarily also reduce these patients' cardiovascular risk.

20. The examining division also referred to documents D10, D11 and D14 (see point 15. above). However, these documents are not comprised within the state of the art under Article 54(2) EPC and are therefore not relevant for assessing the skilled person's expectation at the filing date of the application.

21. The above assessment of the skilled person's expectation (see point 19.) is not altered by the fact that PCSK9 loss-of-function mutations were shown to be associated with lower LDL-C levels and reduced cardiovascular risk. The reduced cardiovascular risk in subjects carrying PCSK9 loss-of-function mutations is concomitant with reduced LDL-C levels (see document D4, page 2, left-hand column, first paragraph). It is however precisely this correlation between lowered LDL-C levels and reduction of cardiovascular risk which was not observed in the specific patient group recited in the claim, i.e. in patients who had experienced an ACS event and, unlike other patients, did not adequately respond to statin therapy (see documents D12 and D13 discussed above). Therefore, in view of the teaching in document D12 and D13, the reduction of cardiovascular risk observed in patients carrying PCSK9 loss-of-function mutations cannot result in the expectation that treatment with an inhibitory PCSK9 antibody could reduce cardiovascular risk in the specific patient group recited in the claim.

22. The decision under appeal cited decision T 239/16, which reads (Reasons 6.5 on page 31): "*The board*

considers that the mere fact that an active agent...is being tested in a clinical study for the treatment...leads to an expectation of success..". This consideration is not absolute but must be understood in the context of decision T 239/16, where it was also held (Reasons 6.6 on page 36) "*...that the mere fact that a clinical study is performed does not as a rule mean that the particular therapeutic effect is always achieved*". The board responsible for the case then continues to explain why, in the particular circumstances of this case, the expectation of the skilled person based on the ongoing clinical study was warranted. In addition, the board recognised that the skilled person could be dissuaded from this expectation by the prior art (Reasons 6.5). It assessed a number of prior-art documents and concluded that "*There is no indication whatsoever in the prior art... that such treatment would fail*". However, in the case at hand the teaching in documents D12 and D13 constitutes such indications. For this reason alone, the reference to decision T 239/16 is not convincing.

23. In view of the above considerations, the board holds that the skilled person could not have had more than a hope that the treatment assessed in the phase 3 clinical trial disclosed in document D4 would succeed in achieving its goal of reducing cardiovascular risk in the treated patients. However, a skilled person's mere hope to succeed is not sufficient to deny inventive step. The claimed subject-matter therefore involves an inventive step when starting from the disclosure in document D15.

Document D4

24. Document D4 discloses that treatment with alirocumab reduces the levels of LDL-C and other atherogenic lipoproteins in high cardiovascular risk patients inadequately controlled with statin therapy (see e.g. the studies summarised in Tables 2 and 3 of document D4 and page 5, left-hand column, last paragraph) and that a phase 3 clinical trial for evaluating whether alirocumab had an effect on the occurrence of cardiovascular events in these patients is ongoing (see point 7. above; see last full sentence on page 10 and last entry in Table 4 of document D4).

25. The claimed subject-matter differs from this teaching in that the actual treatment with alirocumab for reducing the cardiovascular risk in these patients is claimed. The objective technical problem may be formulated as the provision of a treatment for reducing cardiovascular risk in such patients using alirocumab.

26. To decide whether the solution to this problem presented in the claim is inventive, it has to be assessed whether the skilled person would reasonably have expected that the treatment recited in the claim would reduce cardiovascular risk in high cardiovascular risk patients inadequately controlled with statin therapy. Hence, when document D4 is selected as the starting point for assessing inventive step, the same considerations on the outcome of the ongoing clinical trial disclosed in document D4 assessed in points 14. to 23. above apply.

27. Consequently, the claimed subject-matter also involves an inventive step when the disclosure in document D4 represents the closest prior art.

28. Therefore, based on the available evidence and irrespective of whether document D15 or document D4 was selected as closest prior art, the subject-matter of claim 1 involves an inventive step (Article 56 EPC).

Remittal (Article 111(1) EPC)

29. Pursuant to Article 111(1) 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.

30. It is the primary function of appeal proceedings to give a judicial decision on the correctness of the decision under appeal (see Case Law of the Boards of Appeal, 10th edition 2022, section V.A.1.1, second paragraph and the decisions referred to therein; see Article 12(2) RPBA 2020).

31. With respect to the set of claims of auxiliary request 1 underlying the appeal, the examining division took a reasoned decision only on inventive step starting from document D4 or D15 as closest prior art (see section II.), and the board has reviewed this decision (see points 7. to 28. above).

32. Not remitting the case to the examining division would therefore require the board to carry out an examination of the application on possible further inventive-step objections and each of the other requirements of the EPC not considered by the examining division, rather than review the contested decision in a judicial manner, which is the primary purpose of appeal proceedings (see point 30. above).

33. In view of these considerations, the board concludes that special reasons within the meaning of Article 11 RPBA 2020 present themselves for remitting the case to the department whose decision was appealed.

34. Accordingly, in line with the appellants' request, 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:

L. Malécot-Grob B. Claes

Decision electronically authenticated