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Language of the proceedings: EN

Title of invention:
High affinity human antibodies to PCSK9

Patent Proprietor:
Regeneron Pharmaceuticals, Inc.

Opponent:
Furo Ventures B.V.

Headword:
Anti-PCSK9 antibodies/REGENERON

Relevant legal provisions:
EPC Art. 56, 87, 123(2)

Keyword:

Amendments - added subject-matter (no)
Priority - (yes)
Inventive step - (yes)

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Case Number: T 1669/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 3 November 2022

Appellant: (Opponent)	Furo Ventures B.V. Willemsplein 2 5211 AK s'Hertogenbosch (NL)
Representative:	Breuer, Markus Sendlinger Straße 29 80331 München (DE)
Respondent: (Patent Proprietor)	Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 15 April 2019 concerning maintenance of the European Patent No. 2358756 in amended form.**

Composition of the Board:

Chairman	P. de Heij
Members:	A. Chakravarty
	R. Hauss

Summary of Facts and Submissions

I. The appeal of the opponent (appellant) lies from the interlocutory decision of the opposition division that the European patent No. 2 358 756, as amended in the form of the main request, met the requirements of the EPC. The patent was originally filed as an international application, published as WO 2010/077854 (the application as filed or the application).

II. The patent proprietor is respondent to this appeal.

III. In the decision under appeal, the opposition division considered objections under Article 123(2) EPC, Article 83 EPC and Article 56 EPC. In the context of deciding on inventive step, the opposition division held that the claims of the main request were entitled to claim priority from the first priority document. As a consequence, document D12 was not prior art under Article 54(2) EPC.

IV. With the statement of grounds of appeal, the appellant submitted documents D22 to D26. The appellant's objections maintained in appeal related to added subject-matter and lack of inventive step.

V. The respondent replied to the appellant's statement of grounds of appeal and resubmitted sets of claims of the main request (the claim request held allowable by the opposition division) and of auxiliary requests 1 to 3 (auxiliary requests 3 to 5 filed before the opposition division).

VI. Claims 1, 7 and 8 of the set of claims held allowable by the opposition division (main request) read:

"1. A human antibody or antigen-binding fragment of a human antibody that specifically binds human proprotein convertase subtilisin/kexin type 9 (hPCSK9) comprising a HCVR of SEQ ID N0:90 and a LCVR of SEQ ID NO: 92.

7. An antibody or antigen-binding fragment of an antibody according to claim 1 or claim 2 for use to attenuate or inhibit a PCSK9-mediated disease or condition in a subject, wherein the PCSK9-mediated disease or condition is hypercholesterolemia.

8. Use of an antibody or antigen-binding fragment of an antibody according to claim 1 or claim 2 in the manufacture of a medicament for use to attenuate or inhibit a PCSK9-mediated disease or condition in a subject, wherein the PCSK9-mediated disease or condition is hypercholesterolemia."

VII. The following documents remain relevant to this decision.

D1: US 61/122,482 (earliest priority document of the patent in suit, filed 15 December 2008)
D7: WO2008/125623
D8: WO2008/057459
D12: WO2009/026558
D20: Y.G. Ni *et al*, "*A Proprotein convertase subtilisin-like/kexin type 9 (PCSK9) C-terminal domain antibody antigen binding fragment inhibits PCSK9 internalization and restores LDL-uptake*", 19 February 2010, JBC PAPERS in Press, 1-20
D23: Hoogenboom, H.R. (1997) TIBTECH 15:62
D24: Yang W.P. et al (1995) J. Mol. Biol. 254:392

VIII. Oral proceedings before the board were held as scheduled. At the end of the oral proceedings, the Chairman announced the board's decision.

IX. The anti-PCSK9 antibody H1H316P (or "316P") (HCVR/LCVR SEQ ID NO: 90/92), disclosed in the patent under appeal, is an embodiment falling within the definition of claim 1. It is also known as alirocumab, see reply to the statement of grounds of appeal, point 2.2.

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

Main request
Amendments (Article 123(2) EPC) - claims 7 and 8

Claims 7 and 8 of the main request comprised added subject-matter because the application as originally filed did not directly and unambiguously disclose an antibody having the claimed sequences (SEQ ID Nos. 90 and 92) in combination with its use for the treatment of hypercholesterolemia. This subject-matter could only be obtained by making an undisclosed selection from two lists: a list of various antibodies and a list of various diseases.

Furthermore, there was a discrepancy between the first and the second sentence in paragraph [0118] of the application. The first sentence referred to treatment of "*hypercholesterolemia associated with a variety of conditions involving hPCSK9*", not to treatment of hypercholesterolemia as such. In view of this discrepancy there was no direct and unambiguous disclosure of the treatment of hypercholesterolemia as such, without a further limitation of the disease.

Priority (Article 87 EPC)

The subject-matter of the main request was not entitled to the claimed priority from document D1, since document D1 disclosed an antibody as claimed only in combination with a specific K_D value and as "fully human antibodies" which referred to antibodies without mutations.

The respondent's view that the affinity value below 20nM was an inherent feature due to the presence of the defined variable regions was incorrect. The group of possibilities falling under the definition used in the claim was so broad that it would be clear to the skilled person that they included antibodies with different affinities.

Admittance of documents D23 and D24

The admittance of documents D22, D25 and D26 was not requested but it was requested to admit documents D23 and D24 into the proceedings.

Documents D23 and D24 had been filed in direct response to statements made by the respondent during the oral proceedings of 20 March 2019 and the incorrect conclusions drawn from them by the opposition division.

The present claim request had been filed only two weeks before the first-instance oral proceedings. Documents D23 and D24 could therefore not have been filed earlier than with the grounds of appeal.

The documents were *prima facie* relevant and well-known to the respondent. They corroborated that at the

priority date improving affinity of antibodies was mere routine.

Inventive step (Article 56 EPC)
Claim 1

Document D8 as closest prior art

The opposition division had taken document D8 to represent the closest prior art for the claimed invention. Document D8 disclosed antibody antagonists of human PCSK9.

The opposition division had considered that "*the antibody of the patent have* [sic] *been shown to bind PCSK9 considerably more strongly than the Control 1/ 3CX4B08 and 1G08 of D8*" (see decision under appeal, point 4.7) but had ignored the fact that the Fab 1CX1G08 had mean K_D of about 550 pM, which was well below the reported K_D value of alirocumab of about 580 pM. The reasoning used in the decision under appeal to dismiss this was clearly incorrect. Contrary to the opposition division's view a valid comparison between Fab 1CX1G08 and the claimed antibody was possible. The skilled person would understand that Fab 1CX1G08 had a comparable affinity and IC_{50} to alirocumab. The patent proprietor had not provided any experimental evidence directly comparing Fab 1CX1G08 and had used a very indirect way to dismiss the affinity/IC_{50} results of said Fab.

The objective technical problem to be solved was 'the provision of an alternative antibody having high affinity for hPCSK9 and showing high inhibition of cellular LDL uptake'.

The claimed antibody bound to a target that was already known and was an obvious alternative to the known antibodies to this target.

Even if the reasoning of the opposition division that the claimed antibody had better binding properties than the antibodies disclosed in document D8 were accepted, the claimed antibody still lacked an inventive step, since the skilled person starting from the antibodies disclosed in document D8 knew how to prepare antibodies against a target such as PCSK9 and how to optimize them. The skilled person would merely have applied routine techniques to generate additional, improved anti-PCSK9 antibodies.

The techniques required to generate such alternative antibodies were disclosed in document D8. The skilled person would not have read the specific examples in isolation but would have taken the entire teaching of the document into account. The general disclosure in document D8 regarding the expected levels of affinity, function and potency of the antibodies and the disclosure of suitable techniques for preparing and selecting improved antibodies, including phage display and functional studies to ensure proper functionality, would have provided the person skilled in the art with a reasonable expectation of success when seeking to obtain alternative or even improved antibodies.

Moreover, the tool-kit of techniques referred to in document D8 would have enabled the skilled person to obtain antibodies providing high inhibition.

Finally, in relation to the question of whether or not the claimed subject-matter actually represented a solution to the objective technical problem, it was

doubtful if antigen-binding fragments, also covered by claim 1, were large enough to block the critical epitope and provide the alleged technical effect of high inhibition across the entire scope claimed.

Document D7 as closest prior art

In relation to the respondent's submission that the patent included evidence of an improved potency of the claimed antibodies compared to the antibodies disclosed in document D7, it was to be noted that this data was not meaningful because a comparison was made between a Fab fragment and a whole antibody. The smaller molecule would have poorer activity due to its smaller size.

Similarly, claim 1 of the main request included in its scope antibody fragments. These would also not possess considerably improved potency comparable to that of the larger antibody used in the Examples in the patent.

In addition, the K_D values reported in document D7 and those reported in the patent were not comparable because of differences between the experiments.

Thus, the claim lacked an inventive step because at least some of the claimed subject-matter did not represent an improvement over the antibodies disclosed in document D7 and therefore was an obvious alternative.

Even if the claimed antibodies were deemed an improvement over those disclosed in document D7, the person skilled in the art knew how to optimise existing antibodies to improve their affinity for their target and/or their potency and that they would have had a

reasonable expectation of producing an improved antibody using these known techniques.

XI. The appellant also submitted a line of argument that if priority was not valid, then the claimed subject-matter lacked an inventive step in the light of document D12. This line of argument is not relevant to the decision in view of the board's decision on the validity of the priority (see point 12., below) and is therefore not reproduced here.

XII. The submissions of the respondent as far as relevant to the present decision are summarised as follows:

Main request
Amendments (Article 123(2) EPC) - claims 7 and 8

The appellant had objected that the application did not directly and unambiguously disclose an antibody having the combination of the claimed sequences (SEQ ID 90 and 92) in combination with its use for the treatment of hypercholesterolemia because, to arrive at the claimed subject matter, a selection had to be made from two lists: the list of various antibodies and the list of various diseases. This objection was without merit.

The application singled out hypercholesterolemia as the prime disease to be treated with the anti-PCSK9 antibody or fragment of the invention at paragraph [0118] which read "*The anti-PCSK9 antibodies or antibody fragments of the invention are particularly useful for the treatment of hypercholesterolemia and the like*".

The specific human antibody with an HCVR of SEQ ID NO: 90 and an LCVR of SEQ ID NO:92 was also singled out

throughout the application as filed, for example in paragraph [0016] (final sentence). Furthermore, antibodies with these variable region sequences were highlighted throughout the Examples as the most preferred antibodies of the invention. Paragraph [0126] indicated that the antibody "316P" has "HCVR/LCVR SEQ ID NO:90/92", indicating that this was the part of the antibody that was considered important in the context of the examples.

Moreover, there was no discrepancy between the first and the second sentence of paragraph [0118] of the application.

Priority (Article 87 EPC)

The appellant had alleged that the claimed subject-matter was not entitled to priority due to the absence of an affinity limitation in the claims. However, the opposition division had been right to dismiss this objection on the grounds that an antibody with the variable region sequences specified in claim 1 inherently has an affinity in the range specified in D1 (paragraph 3.9 of the decision) due to its structure. The opponent had advanced no reasoning or evidence that would call this into question. It was implausible that any mutation in the constant region of the antibody would lead to a 35-fold loss in affinity. The high affinity of the claimed antibodies was a result of the particular variable region defined in the claim.

In support of this view, it should be noted that both the priority application and the patent disclosed that a human antibody with the variable region sequences recited in claim 1 bound to hPCSK9 with an affinity far stronger than 20 nM minimum. This was true regardless

of the conditions used to measure affinity. The evidence in the examples of the patent also supported this view, since all antibodies tested had K_D values lower than the 20 nM.

Admission of documents D23 and D24

Claim 1 of the claim request was identical to claim 1 of the patent as granted. The appellant had not provided a single concrete example of new arguments that had been raised at the first-instance oral proceedings that were addressed by the documents. The filing of the documents only in appeal had not been justified.

Inventive step (Article 56 EPC)
Claim 1

Document D8 as closest prior art

The claimed antibody and antibody fragments were clearly distinguished from those disclosed in document D8 in terms of their sequence. In turn, the variable region sequences of the claimed antibody conferred superior technical effects over the antibodies of D8. These superior technical effects were demonstrated in the Examples of the patent. The claimed antibody showed higher affinity. In addition and at the very least, the claimed antibody was significantly more potent than any of the antibodies of document D8.

The patent itself contained a direct comparison between the best of the antibodies of document D8 and the claimed antibody, revealing the technical advantages of the claimed antibody in side-by-side, controlled experiments. In Example 4 of the patent, the 316P

antibody was tested alongside an antibody referred to as "Control I" which was D8's 3CX4B08 antibody. From the examples in document D8, it was apparent that 3CX4B08 was representative of the best that could be achieved in terms of inhibition of PCSK9's effects on cellular LDL uptake (see D8, page 44, lines 5-20). Table 23 of the patent reported that, when 3CX4B08 was tested alongside 316P, the latter was at least an order of magnitude more potent at reversing PCSK9's inhibition of cellular LDL uptake. The other examples supported this thesis. For instance, Example 8 showed that the inhibition of binding between hPCSK9 and hLDLR was >1000-fold greater using 316P than Control I (Table 14, page 24 of the patent; IC_{50} of <125 pM for 316P versus >100,000 pM for Control I).

Document D20 (a post-published document reporting the findings of D8 in relation to the less potent 1CX1G08) reported that '*1G08 does not affect the PCSK9-LDLR Interaction*' (see page 4, right hand column). Thus, the 1CX1G08 antibody was shown as not only much less potent than the claimed antibody in inhibiting the PCSK9-LDLR interaction, but in fact did not inhibit this interaction at all.

With regard to the appellant's references to certain IC_{50} values reported in document D20 for the 1G08 antibody and their comparison with IC_{50} values reported in the patent, this was inappropriate. An IC_{50} value referred to the concentration of antibody at which a 50% inhibition of a certain property is achieved. However, IC_{50} values were entirely dependent on the particular type of inhibition being measured, the specific assay setup and the concentration of the antibody and other components of the assay. IC_{50} values could not be compared between experiments. The only

appropriate comparisons were side-by-side comparisons, as the patentee had conducted.
As regards the specific IC_{50} values reported in D20, the value of 4 nM (page 4, right hand column, first paragraph) was actually an IC_{50} value for self-competition – not an LDL uptake assay at all. Accordingly, it made no sense to compare this value with the IC_{50} value for LDL uptake reported in the patent. The IC_{50} value of 50 nM reported in the following paragraph of document D20 was for an assay conducted with HEK cells – a different cell line from the HepG2 cells used in the LDL uptake assay of the patent (see paragraph [0132]). The value reported in document D8 for HepG2 cells was 150 nM [sic: the value is actually reported in document D20], significantly lower [sic: higher] than the 21 nM value reported in Table 23 of the patent for 316P. Even then, the two values were not directly comparable, since the assay conditions used in document D8 [sic: D20] were not reported.

The technical problem

The claimed antibody had improved affinity and potency over the antibodies of document D8. Thus, the objective technical problem was the provision of an improved antibody with high potency and high affinity. The data in the patent showed that this problem had been solved.

Obviousness

At the relevant date of the patent, it would not have been obvious to the skilled person that an antibody could be generated with the specific variable region sequences recited in the claims and having such

improved affinity and potency in inhibiting the PCSK9-LDLR interaction.

Document D7 as closest prior art

As was the case with respect to the antibodies disclosed in document D8, the claimed antibodies and antibody fragments were clearly distinguished from those of document D7 in terms of both their sequence and their superior technical effects. These superior technical effects included both higher affinity and higher potency.

The claimed antibody and antibody fragments had a significantly higher affinity for PCSK9 compared to the ones disclosed in document D7. The antibody disclosed in document D7's Examples, the H1 Fab, only bound to PCSK9 with a K_D of ~10 nM, while the claimed antibody, 316P, bound to PCSK9 with a much higher affinity, reflected in a K_D of 191 pM.

The claimed antibody and antibody fragments were also significantly more potent in disrupting the interaction between PCSK9 and LDLR and reducing LDL levels. It should be noted that the H1 Fab, at a concentration of 1 µM, only blocked the PCSK9/LDLR interaction by about 30%. Figure 4A of D7 seemed to show a plateauing of the response after about 0.3 µM, suggesting that the H1 Fab would be unlikely to inhibit the interaction by more than 30%, even if the concentration of the Fab were increased.

The 316P antibody of the invention blocked the PCSK9/LDLR interaction with IC_{50} values of less than 125 pM. A concentration of less than 125 pM achieved a reduction in binding of 50%. The assays used in

document D7 and the patent differed, but it was unmistakably clear that the claimed antibody inhibited the binding interaction between PCSK9 and LDLR far more potently than the H1 Fab of document D7.

The technical problem

The objective technical problem was formulated as the provision of an improved antibody against PCSK9, which could better inhibit the PCSK9-LDLR interaction.

Obviousness

The unexpected and beneficial properties of the claimed antibody over those of document D7, in terms of both their affinity and their potency in inhibiting the PCSK9-LDLR interaction, was ample evidence to support a finding of inventive step.

XIII. The appellant requested that the decision under appeal be set aside and that European patent No. 2358756 be revoked in its entirety.

XIV. The respondent requested that the appeal be dismissed, or alternatively, that the patent be maintained on the basis of the claims of one of auxiliary requests 1 to 3 (all filed with the reply to the statement setting out the grounds of appeal). The respondent also requested that the objections of lack of inventive step based on document D7 and document D12 not be admitted into the proceedings, and that documents D22 to D26 not be admitted into the proceedings.

Reasons for the Decision

Main request

Amendments (Article 123(2) EPC) - claims 7 and 8

1. The appellant challenged the opposition division's finding that claims 7 and 8 of the main request met the requirements of Article 123(2) EPC.

2. The appellant's objection was that there was no direct and unambiguous disclosure of the claimed sequences (SEQ ID 90 and 92) in combination with its use for the treatment of hypercholesterolemia in the application.

3. An antibody comprising a HCVR of SEQ ID N0:90 and a LCVR of SEQ ID NO: 92 is disclosed in paragraph [0016] of the application as filed (see final sentence of that paragraph). That the claimed antibodies are useful in the treatment of hypercholesterolemia is disclosed at various locations in the application, in particular in paragraph [0118] the first and second sentence of which read "*The invention provides therapeutic methods in which the antibody or antibody fragment of the invention is useful to treat hypercholesterolemia associated with a variety of conditions involving hPCSK9. The anti-PCSK9 antibodies or antibody fragments of the invention are particularly useful for the treatment of hypercholesterolemia and the like*". Thus, it is apparent that all antibodies disclosed in the application are disclosed being suitable for use in the treatment of hypercholesterolemia. No selection from a list of disorders is needed to arrive at the subject-matter of claim 7 or 8.

4. The appellant further argued that there was a discrepancy between the first and the second sentence in paragraph [0118] of the application and that in view of this, there was no direct and unambiguous disclosure of the treatment of hypercholesterolemia as such, without a further limitation of the disease.

5. The board does not find this argument convincing and can identify no discrepancy in the above-mentioned paragraph. The first sentence of that paragraph does indeed relate to treatment of hypercholesterolemia associated with a variety of conditions involving hPCSK9. However this is not in contradiction to the second sentence which refers to the suitability of the claimed antibodies "*for the treatment of hypercholesterolemia*". Rather than being a contradiction, the first sentence explains why the antibodies and fragments are suitable for treating hypercholesterolemia, namely, because they are anti-PCSK9 and because hypercholesterolemia occurs in conditions involving hPCSK9. There is no discrepancy with the second sentence because this serves as a continuation of the statement in the first sentence and does not imply that the anti-PCSK9 antibodies treat diseases mediated by a different mechanism. This is also reflected in claims 7 and 8 of the main request which do not refer to hypercholesterolemia in general, but only to PCSK9-mediated hypercholesterolemia.

6. In view of the above considerations, the subject matter of claims 7 and 8 meets the requirements of Article 123(2) EPC.

Priority (Article 87 EPC)

7. The appellant considered that document D12 (published 26 February 2009, i.e. before the second priority date of the patent in suit) was comprised in the state-of-the-art for the claimed invention because, in its view, the claims of the main request were not entitled to the first claimed priority (D1, filed 15 December 2008). The claimed subject-matter was not inventive over document D12. It is therefore necessary to decide whether or not the claimed invention is entitled to claim priority from earlier application document D1.

8. The appellant's particular concern was that the claimed antibody had only been disclosed in document D1 in combination with the specific K_D value of 20 nM or less for PCSK9. In this regard the appellant referred to the reference in document D1 (paragraph 4) to "fully" human antibodies, which, in its view, related to antibodies without mutations. In contrast, the claims of the main request, lacking the limitation to "fully" human, included antibodies having mutations which adversely affected their K_D and whose K_D for PCSK9 might therefore be higher than the "20 nM or less" disclosed in document D1.

9. In as far as the appellant argues that the term "human antibody" in claim 1 has a wider scope than the antibodies disclosed in D1 because in the patent the term includes mutant antibodies, this position is rejected. It has not been proven to a satisfactory degree, that a genuine distinction is made in document D1 or the patent between human and fully human antibodies. It is understood that both serve to exclude mouse (or other animal) antibodies and animal/human chimeric antibodies as mentioned in paragraph [0049] of

document D1. But even if such distinction were made, document D1 clearly discloses that the term antibodies includes mutants (see the definition in paragraph [0031]; see also paragraph [0005] explaining that the antibodies may be modified), as it does in the patent. The term human antibody in claim 1 therefore has the same meaning as in document D1.

10. The appellant submitted *i.a.*, that due to the lack of a limitation to "fully" human antibodies "*The group of possibilities claimed by the definition used in the patent is so broad that it is immediately clear to the skilled person that they may very well have different affinities*".

11. The board cannot find this argument convincing. The appellant did not further substantiate its allegation by means of examples or evidence and the position put forward is not self-evident. Moreover, as noted by the respondent, document D1 at paragraph [0049], last sentence reads "*While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region*". The board is persuaded that this statement is correct and that the K_D value of 20 nM or less for PCSK9, i.e. the association coefficient of the claimed antibody with PCSK9 is an inherent property of all molecules defined in the claim because the claim specifies the entire light chain and heavy chain variable regions by their sequence and the binding properties of the antibody are determined by said sequences.

12. In view of the above considerations, the board concludes that the subject-matter of claim 1 validly claims priority from document D1. Thus, document D12 is

not part of the state-of-the-art for the claimed invention and will not be further considered for the assessment of inventive step.

Admission of documents D23 and D24 (Article 12(4) RPBA 2007)

13. The appellant filed documents D23 and D24 with the statement of grounds of appeal with the aim of supporting a line of argument on inventive step, in particular to show that certain techniques were well-known at the relevant date of the patent.

14. Under the in the present case applicable Article 12(4) RPBA 2007, the board has discretion not to take into account documents that could have been filed in the proceedings before the opposition division. In the present case, the topic of inventive step had been raised and extensively discussed in the proceedings before the opposition division, see the opposition division's communication dated 25 May 2018, section 4, and the decision under appeal, section 4. It is noted that claim 1 dealt with in the communication was identical to claim 1 of the present main request.

15. Indeed, the legal and factual framework, in particular the claimed subject-matter and the selection of documents on which the case of lack of inventive step is based, has not changed. The allegation that the filing responded to new developments during the oral proceedings has not been substantiated in any way.
In view of this, the board concluded that both documents could and should have been filed in the proceedings before the opposition division.
In addition, documents D23 and D24 are not considered of particular relevance for the assessment of inventive step because the line of argument based on them,

relating to the expected levels of affinity, function and potency of the antibodies, and the disclosure of suitable techniques for preparing and selecting improved antibodies, including phage display and functional studies to ensure proper functionality, could also be found in document D8.

16. For these reasons, the board decided not to admit documents D23 and D24 into the appeal proceedings.

Inventive step (Article 56 EPC)

Claim 1

Document D8 as closest prior art

17. The appellant was of the view that the subject matter of claim 1 lacked an inventive step in the light of the disclosure in document D8 alone. The appellant had two main lines of reasoning. The first was that document D8 already disclosed antibodies with equivalent properties to the claimed ones and that these latter were therefore mere alternatives that could be routinely obtained by the person skilled in the art. In an alternative line of reasoning, it was argued that even if the claimed antibodies had superior properties, the skilled person would have used routine methods to optimise the known antibodies.

The technical problem

18. The claim is for a human antibody or antigen-binding fragment thereof that specifically binds human PCSK9 and is defined by particular heavy and light chain variable region sequences.

19. Document D8 discloses a number of PCSK9-specific antibodies, termed 1CX108, 3BX5C01, 3CX2A06, 3CX3D02, and 3CX4B08, which dose-dependently inhibited the effects of PCSK9 on LDL uptake (see page 15, lines 22 to 24). These antibodies recognise human PCSK9 and are suitable for use in treating hypercholesterolemia. They differ from the claimed ones in the sequence of the variable regions and as consequence of this also in terms of their binding properties.

20. The patent provides evidence that the claimed antibodies are improved compared to those disclosed in document D8 in terms of both potency, reported as IC_{50} values, and affinity, reported in terms of K_D. In Example 4 of the patent, the 316P (an antibody according to the invention) was tested alongside an antibody "Control I" (3CX4B08 of document D8) and it is shown in Table 5 that at pH 7.4, 316P has a K_D of 191 compared to a K_D of 20000 for 3CX4B08. In Example 11 (Table 23), which reports on the increase of LDL uptake due to anti-hPCSK9 antibodies, it is shown that 316P has an IC_{50} of 21.30 nM, whereas 3CX4B08 has an IC_{50} of >250 nM.

21. That 3CX4B08 is more potent than the other antibodies disclosed in document D8 can be seem from page 44, lines 5 to 20 (of D8), according to which "*1CX1G08 exhibited a 53% inhibition of PCSK9-dependent inhibition of cellular LDL uptake, while 3CX4B08 exhibited a 61 % inhibition*".

22. The appellant questioned whether the antibodies of the invention have improved potency compared to Fab 1CX1G08 disclosed in document D8.

23. According to example 5 of document D8, 3CX4B08 was more potent than 1CX1G08. Thus, the improved potency of 316P over 3CX4B08 holds, *a fortiori* over 1CX1G08. Moreover, the board has noted the respondent's submission that according to document D20, the 1CX1G08 antibody does not inhibit the PCSK9-LDLR interaction at all. The appellant has not provided a convincing counter argument. Thus the board accepts that the claimed antibodies show significantly improved potency over those disclosed in document D8.

24. The appellant also questioned whether the claimed antibodies had improved affinity over those of document D8. However, this question need not be dealt with because inventive step can be assessed on the basis of improved potency alone.

25. In view of the above differences and their technical effect, the problem solved by the claimed subject-matter can be formulated as "provision of an anti-hPCSK9 antibody having significantly improved potency".

Obviousness

26. The question to be answered in assessing the obviousness of the claimed subject-matter is whether or not the skilled person, starting from the disclosure in document D8, and in particular from antibodies 3CX4B08 or 1CX1G08, would have expected to be able to produce an anti-hPCSK9 antibody which was significantly better at reversing the inhibitory effect on LDL uptake by PCSK9 protein than those antibodies (i.e. a significantly more potent antibody).

27. As set out in point 23. above, the board is persuaded that the claimed antibodies are significantly improved

in terms of potency compared to those in document D8. While the board accepts the respondent's position that there were techniques available to the skilled person to optimise and improve the affinity and/or potency of monoclonal antibodies, it has seen no evidence that the skilled person had a reasonable expectation of producing antibodies of significantly increased potency comparable to that of the claimed antibodies.

Admission of a line of argument relating to smaller-sized antibodies (Article 13(2) RPBA)

28. The appellant presented a line of argument that not all embodiments falling within the scope of the claim shared the same improved properties. This argument was based on the idea that an antigen-binding fragment of an antibody would have poorer activity due to its smaller size. It was doubtful if it was large enough to block the critical epitope. This line of argument had not been presented in writing, which was conceded by the appellant.

29. Under Article 13(2) RPBA, any amendment to a party's appeal case made after the 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.

30. The board decided to exclude this line of argument from the appeal proceedings under Article 13(2) RPBA. The appellant stated that the reason for the amendment of the case represented by the above-mentioned line of argument was that it was in response to submissions of the respondent also made for the first time at oral proceedings. However, the board concluded that the line

of argument was in fact made in response to the observation of the respondent that for antibodies to exert their effect, it is essential that they bind the right epitope. This observation, while correct, cannot have confronted the appellant with a relevant new issue as it addresses the function of the claimed antibodies which was already central to the parties' cases before the opposition division. Therefore, any doubts whether antibody fragments would be able to bind and block the correct epitope could have been raised in the written submissions of the appellant. Thus, the board concluded that there were no exceptional circumstances which might justify admitting the amendment to the appellant's case represented by this line of argument, into the appeal proceedings at the hearing.

Document D7 as closest prior art

31. The board decided that the line of argument of lack of inventive step based on document D7 representing the closest prior art was part of the appeal proceedings based on the substantiation given by the appellant's specific reference to the notice of opposition. Since this line of argument was not successful, further reasons for its admittance need not be given.

32. The appellant's line of argument taking the disclosure in document D7 to represent the closest prior art, mirrors that given in respect of document D8. In other words, the appellant first argued that there was no improvement in terms of affinity compared to the antibodies disclosed in document D7 and secondly, the person skilled in the art knew how to optimise existing antibodies to improve their affinity for their target and/or their potency and that they would have had a

reasonable expectation of producing an improved antibody using these known techniques.

33. At oral proceedings, the appellant put forward a line of argument that the comparisons between the potency of the H1 Fab disclosed in document D7 (see Example 5) and the 316P embodiment of the claim (see Example 8 of the patent), that showed that the latter was more potent, could not be relied upon because they were made between a Fab fragment (in document D7) and a whole antibody (in the patent). The smaller molecule would have poorer activity due to its smaller size.

34. This line of argument was not admitted into the proceedings. The reasons set out in point 30. above apply *mutatis mutandis*. It is therefore not taken into account.

35. No other reasons were provided by the appellant to substantiate their view that the claimed antibodies do not have increased potency compared to those disclosed in document D7. Thus, the board accepts that, as put forward by the respondent, even taking differences in assay into account, the claimed antibody (and antigen-binding fragment) inhibits the binding interaction between PCSK9 and LDLR far more potently than the H1 Fab disclosed in document D7. In particular, document D7 shows that the H1 Fab, at a concentration of 1 micromolar, was able to block the PCSK9/LDLR interaction by about 30% (see Example 5, page 66, and Figure 4A). In comparison,the 316P antibody (an embodiment of claim 1) blocks the PCSK9/LDLR interaction with IC_{50} values of less than 125 picomolar (Example 8, Table 14 of the patent). That is, a concentration of <125 pM (i.e. of the order of 0.0001 µM) achieves a reduction in binding of 50%. The patent

also shows that the claimed antibody is able to reverse the inhibitory effect of PCSK9 to a far greater extent than is possible with the H1 Fab of document D7. Antibody 316P was shown to increase LDL uptake with an IC_{50} of 21.30 nM. In contrast, in document D7 it is disclosed that concentrations of 0.5 µM - 2 µM of H1 Fab were required to achieve an increase in cell surface LDLR levels (Figure 4B) or an increase in LDL uptake (Figure 4C).

36. The reasons why the board does not find the second line of argument convincing are the same as those given in the reasoning concerning document D8 as a starting point for an assessment of inventive step, see point 27. above.

37. In view of the above considerations, the objections raised by the appellant did not convince the board and the appeal is not successful.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

I. Aperribay P. de Heij

Decision electronically authenticated