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Datasheet for the decision of 6 December 2023

Case Number:	T 1927/22 - 3.3.04
Application Number:	12761864.3
Publication Number:	2756004
IPC:	C07K16/40, A61P3/06, A61K39/395, A61K39/00
Language of the proceedings:	EN

Title of invention:

Inhibitor of proprotein convertase subtilisin kexin-9 (PCSK9) for use in reducing lipoprotein(a) levels

Patent Proprietor:

Regeneron Pharmaceuticals, Inc.

Opponents:

Amgen Inc.
Boehmert & Boehmert Anwaltspartnerschaft mbB

Headword:

PCSK9 inhibitor for reducing Lp(a)/REGENERON

Relevant legal provisions:

EPC Art. 100(a), 100(b), 54, 56
RPBA 2020 Art. 12(2), 12(4)

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Keyword:

Novelty - main request (yes)
Amendment to case - argument - reasons for submitting amendment in appeal proceedings (yes)
Sufficiency of disclosure - main request (yes)
Inventive step - main request (yes)

Decisions cited:

T 0293/07, T 0847/07, T 1545/08, T 1011/17

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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 1927/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 6 December 2023

Appellant: (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)
Appellant: (Opponent 1)	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 (US)
Representative:	Dörries, Hans Ulrich df-mp Fünf Höfe Theatinerstrasse 16 80333 München (DE)
Party as of right: (Opponent 2)	Boehmert & Boehmert Anwaltspartnerschaft mbB Pettenkoferstr. 22 80336 München (DE)
Representative:	Engelhard, Markus Boehmert & Boehmert Anwaltspartnerschaft mbB Pettenkoferstrasse 22 80336 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 16 August 2022 concerning maintenance of European Patent No. 2 756 004 in amended form**

Composition of the Board:

Chairman	A. Chakravarty
Members:	B. Rutz
	R. Romandini

Summary of Facts and Submissions

I. The appeals by the patent proprietor (appellant I) and opponent 1 (appellant II) lie from the interlocutory decision of the opposition division that European patent No. 2 756 004, entitled "*Inhibitor of proprotein convertase subtilisin kexin-9 (PCSK9) for use in reducing lipoprotein(a) levels*", met the requirements of the EPC in amended form according to auxiliary request 12a.

II. The patent had been opposed by two opponents on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and of Article 100(b) EPC.

III. In the decision under appeal, the opposition division held that the invention to which claim 1 of the main request (patent as granted) and claim 1 of auxiliary requests 1 to 23 (not including 12a) related was not sufficiently disclosed.

IV. With its statement of grounds of appeal, the patent proprietor refiled sets of claims of the main request (patent as granted) and of auxiliary requests 12 and 12a and a declaration of Prof. Di Angelantonio (D148).

V. With its statement of grounds of appeal, opponent 1 submitted documents D145 (renumbered as D153 by the board), 145a (renumbered as D153a by the board), D146, D146a, D147 and an Annex A and reiterated its request for acceleration.

VI. Opponent 2 withdrew its appeal and is party as of right to the proceedings.

VII. With its reply to opponent 1's appeal, the patent proprietor filed sets of claims of the main request (patent as granted) and of auxiliary requests 1 to 35 wherein the main request and auxiliary requests 1 to 8, 10, 12, 14, 16, 18 to 21, 23, 25, 27 to 30, 32 and 34 are identical to the main request (patent as granted) and auxiliary requests 1, 2, 5, 10 to 12, 12a, 13, 14, 17, 22, 23, 29, 34, 35, 41, 46, 47, 48 to 51, 52 and 53, respectively, filed during the opposition. Auxiliary requests 9, 11, 13, 15, 17, 22, 24, 26, 31, 33 and 35 were newly filed (see Table on page 81 of the reply to the appeal of the patent proprietor). The patent proprietor further filed documents D148 (renumbered by the board as D150) and D149 (renumbered by the board as D151).

VIII. With its reply to the patent proprietor's appeal, opponent 1 filed document D149.

IX. With the letter dated 5 August 2023, opponent 1 filed document D152.

X. The board appointed oral proceedings, as requested by the parties and in a communication under Article 15(1) RPBA 2020, informed them of its preliminary opinion.

XI. With the letter dated 15 November 2023, the patent proprietor filed document D153 (renumbered by the board as D154).

XII. Claim 1 of the main request (patent as granted) reads as follows:

"1. A pharmaceutical composition comprising a PCSK9 inhibitor for use in reducing lipoprotein(a) (Lp(a))

levels in a patient who exhibits a serum Lp(a) level above 30 mg/dL and who is diagnosed with or identified at being at risk of developing a cardiovascular disease or disorder prior to or at the time of administration of the composition, or who is diagnosed with or identified as being at risk of developing a thrombotic occlusive disease or disorder prior to or at the time of administration of the composition; and wherein the PCSK9 inhibitor is an antibody or antigen-binding fragment thereof that specifically binds PCSK9."

XIII. At the end of the oral proceedings the Chairman announced the board's decision.

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

D1 G. Swergold et al., "*REGN727/SAR236553, A FULLY HUMAN PROPROTEIN CONVERTASE SUBTILISIN KEXIN 9 (PCSK9) MONOCLONAL ANTIBODY: EFFECTS ON SAFETY AND LIPID AND LIPOPROTEIN PROFILES WHEN ADMINISTERED SUBCUTANEOUSLY*", presented on April 3, 2011 and published in JACC 57(14), April 5, 2011

D2 E. A. Stein et al., "*Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol*" N Engl J Med 366 (12), 2012, 11008-1118

D2a E. A. Stein et al., N Engl J Med, 366(12), 2012, Supplementary Appendix

D3 US 2010/0166768

D4 S. N. 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", N Am Coll Cardiol. 45(10), 2005, 1611 -1619

D11 I. Gouni-Berthold and H. K. Berthold, "*Lipoprotein(a): Current Perspectives*" Current Vascular Pharmacology 9(6), 2011, 682-692

D20 S. van Wissen et al., "*Long term statin treatment reduces lipoprotein(a) concentrations in heterozygous familial hypercholesterolaemia*" Heart 89, 2003, 893-896

D22 K. Parhofer, "*Lipoprotein(a): Medical Treatment Options for an Elusive Molecule*" Current Pharmaceutical Design 17(9), 2011, 871-876

D23 NCT012884443 phase 2 trial, v10, (September 2, 2011), Excerpt from clinical trials.gov, htttps://clinicaltrials.gov/ct2/history/NCT01288443?V_10=View#StudyPageTop

D61 G. Lippi and G. Targhert, "*Optimal Therapy for the reduction of lipoprotein(a)*", Journal of Clinical Pharmacy and Therapeutics 37, 2011,1-3

D62 B. G. Nordestgaard et al., "*Lipoprotein(a) as a cardiovascular risk factor: current status*", European Heart Journal 31, 2010, 2844-2853

D64 Declaration Emanuele Di Angelantonio, dated 10 March 2021

D63 V. Bermúdez, et al., "*Lipoprotein(a): From Molecules to Therapeutics*", American Journal of Therapeutics 17, 2010, 263–273

D94 F. Krempler et al., "*Studies on the Role of Specific Cell Surface Receptors in the Removal of Lipoprotein (a) in Man*", J. Clin. Invest. 71, 1983, 1431-1441

D103 S. L. Hofmann et al., "*Overexpression of Human Low Density Lipoprotein Receptors Leads to Accelerated Catabolism of Lp(a) Lipoprotein in Transgenic Mice*", J. Clin. Invest. 85, 1990, 1542-1547

D104 G. Utermann et al., "Defects in the low density lipoprotein receptor gene affect lipoprotein (a) levels: Multiplicative interaction of two gene loci associated with premature atherosclerosis", PNAS USA 86, 1989, 4171-4174

D106 H. G. Kraft, "Lipoprotein(a) in Homozygous Familial Hypercholesterolemia", Arterioscler Thromb Vasc Biol 20, 2000, 522-528

D110 Antwort von Prof. Dr. med. K. Parhofer, "*Nach Bypass-Op. fast alle Lipide im grünen Bereich - Aber Lp(a) ist zu hoch, was kann man da tun?*", MMW-Fortsch. Med. 21,2011

D115 WO2009/026558

D116 WO2010/077854

D133 E. Anuurad et al., "*Lipoprotein(a): A Unique Risk Factor for Cardiovascular Disease*", Clin. Lab. Med. 26, 2006, 751-772

D148 Declaration of Prof. Emanuele Di Angelantonio, dated 29.12.2022

D150 (former D148) European Medicines Agency, Assessment report: Repatha, 2015

D154 (former D153) Declaration Prof. Parhofer, dated 13.11.2023

XV. Appellant I's (patent proprietor's) submissions relevant to the decision are summarised as follows:

Main request (patent as granted)
Claim construction - claim 1

The claims related to pharmaceutical compositions comprising PCSK9 inhibitors, and more specifically to antibodies against PCSK9, for a specific new therapeutic use, namely reducing Lp(a) levels. The patients who were to be treated had to:
(a) have a serum Lp(a) level above 30 mg/dL; AND either
(b) be diagnosed with or identified at being at risk of a cardiovascular disease or disorder;
OR
(c) be diagnosed with or identified as being at risk of developing a thrombotic occlusive disease or disorder.

As acknowledged by experts in the field before the priority date, lowering Lp(a) levels in patients with elevated levels of this lipoprotein was considered to be a therapeutic intervention (see e.g. documents D11, D61, D62, D63).

Admission of new arguments by the patent proprietor (12(4) RPBA)

During oral proceedings, the opposition division considered only the median values in Table 3B and concluded from these that the invention lacked sufficient disclosure. This was in contrast to its preliminary opinion where it had found the anti-PCSK9 antibody worked also in "diet only" subjects, and that the claims were enabled across their full scope. It had not been possible to react appropriately to this new interpretation of the data in Table 3B during the oral proceedings.

Disclosure of the invention (Article 100(b) EPC)

The technical effect specified in the claims was the reduction of elevated Lp(a) levels, and this effect had been clearly demonstrated in the clinical trials disclosed in the Examples of the patent (see e.g. Example 2, Tables 3A and 3B). Furthermore, Lp(a) levels of >30 mg/dL were well understood to confer a risk of CVD at the priority date, and it was therefore more than plausible that lowering such elevated Lp(a) levels would confer a benefit in terms of reduction of CVD risk.

Data from a small-scale clinical trial were provided in Table 3B of the patent, demonstrating a significant reduction over placebo in Lp(a) levels in patients not treated with statins. Table 3B of the patent demonstrated a lowering of Lp(a) levels over placebo, which is the relevant consideration for demonstrating therapeutic efficacy.

The data in Table 3B also demonstrated an average lowering over baseline Lp(a) levels when the median percentage reduction in Lp(a) over baseline was calculated, as illustrated in document D2/D2a (which contained a post-published disclosure of the data in the patent) and as explained in the analysis of the Table 3B data by Prof. Di Angelantonio in document D148.

Novelty (Article 100(a) EPC and Article 54 EPC)

The reduction in Lp(a) levels was a new therapeutic use, underpinned by a new technical effect which defined a new clinical situation, and the claims were therefore novel over the disclosure in documents D3, D23 and also D115 and D116, should the latter be admitted into the proceedings.

Documents D3 and D23 did not mention of Lp(a) at all, and did not provide any indication that anti-PCSK9 antibodies were capable of reducing Lp(a) levels. Also documents D115 and D116, if admitted into the proceedings did not mention Lp(a).

Inventive step (Article 100(a) EPC and Article 56 EPC)

Opponent 1's attempt to start the analysis of inventive step from an ambiguous passing reference to PCSK9 inhibitors in document D110 showed impermissible use of hindsight. Document D110 did not contain a credible teaching that PCSK9 inhibitors lower Lp(a) levels. It provided no evidence for the alleged Lp(a) lowering effects of the agents in development, nor even a reference list so that the skilled person might cross-check the passing statement. Furthermore, the statement was directly contradicted by other statements of the

same author, Prof. Parhofer, in document D22, where he indicated that the effects of PCSK9 inhibitors on Lp(a) levels were "unknown" (see document D22, Table 3, page 874. Also the suggestion to analyse inventive step starting from document D3 was inappropriate because it did not even mention Lp(a).

The results reported in the patent demonstrating an Lp(a) lowering effect of anti-PCSK9 antibodies were entirely unexpected in light of the biology of Lp(a). At the priority date, the skilled person would not have had any reason to expect that an anti-PCSK9 antibody could lower Lp(a) levels, nor did the prior art provide any scientific rationale for testing this hypothesis, let alone make it obvious to try. In particular, given that statins, in some studies, had been shown to increase Lp(a) levels despite the upregulation of LDLR levels by these drugs, the skilled person might well have expected (if they had considered PCSK9 inhibitors with reference to Lp(a) levels at all) that they would have the very opposite of the desired effect, i.e. that they would increase Lp(a) levels, let alone having a reasonable expectation of success that an anti-PCSK9 antibody could lower Lp(a) levels.

It was highly surprising that anti-PCSK9 antibodies, which were known to work (on LDL-C) by increasing cell surface LDLR levels, could trigger the marked and sustained reduction in plasma Lp(a) levels that is shown in the patent.

XVI. Appellant II's (opponent 1's) submissions relevant to the decision are summarised as follows:

Main request (patent as granted)
Claim construction - claim 1

The patient population identified in claim 1 was identical to or at least significantly overlapping with patients suffering from hypercholesterolemia (see dependent claims 4 and 5). This was due to the fact that the claims did not require a connection between an elevated Lp(a) level and the risk or diagnosis of cardiovascular disease (CVD) or thrombotic occlusion disease (TOD).

The claim neither explicitly nor implicitly required a causal link between serum Lp(a) levels above 30mg/dL on the one hand, and CVD or TOD or the treatment thereof on the other. The opposition division had recognized that an accepted mechanism leading to CVD and TOD was a high LDL-C level, causing hypercholesterolemia, for which PCSK9 inhibitors were already a known treatment. Therefore, an unambiguous connection between the reduction of Lp(a) and the alleged treatment of CVD or TOD was required to define the alleged new therapeutic treatment vis-à-vis the prior art.

Furthermore, Lp(a) was not a risk factor for many subjects encompassed by the claims ("diagnosed with or at risk of developing CVD or TOD"):

- Lp(a) was not a risk factor in subjects having well-controlled LDL-C levels
- Lp(a) was not a risk factor in African-Americans (or at best only at extremely high levels)
- An Lp(a) level of 30 mg/dL was not a cut-off that ensured the treated individual (or group of

individuals) would have a reduced risk in respect of the conditions recited in the claims

- there were many examples of diseases that are classified as CVD or TOD for which Lp(a) was not a risk factor, such as stroke, peripheral arterial obstructive disease (PAOD), venous thromboembolism (VTE) and cardiovascular diseases caused by high blood pressure, smoking or diabetes
- there were serious doubts in the art as to whether the small reductions of Lp(a) achievable with PCSK9 inhibitors translated into any clinical benefit

According to the proprietor, the claims merely promised a reduction of the Lp(a) level (see page 2, sixth paragraph of the Minutes).

The opposition division's conclusion that claim 1 of the patent as granted (main request), defined a treatment by therapy in the sense of Article 53(c) EPC was wrong and as a result, the claim had to be construed as being directed to pharmaceutical compositions that were merely suitable for reducing Lp(a) levels in certain patients.

Novelty (Article 100(a) EPC and Article 54 EPC)

The claim lacked novelty over the disclosure in the prior art, in particular over each of documents D3, D23, D115 and D116 which disclosed PCSK9 inhibitors that were suitable for reducing Lp(a) levels.

Admission of new arguments by the patent proprietor (12(4) RPBA)

The proprietor's mathematical arguments about Table 3B were new arguments that were not presented before the

opposition division. In the statement of grounds of appeal, the proprietor for the first time had raised the theory that Table 3B's explicit demonstration of an absolute increase over baseline Lp(a) should be ignored in favor of a series of calculations based on the median percentage lowering over baseline Lp(a) levels and on purported common general knowledge about Lp(a) levels. These arguments were a complex amendment to the proprietor's case in view of the necessary calculations. The new arguments should not be admitted into the proceedings in accordance with Article 12(4) RPBA.

Disclosure of the invention (Article 100(b) EPC)

The only data in the patent relating to patients that were not on a therapeutic statin regimen were in Table 3B which showed that Lp(a) levels increased from 34 mg/dL to 39 mg/dL in patients treated with the PCSK9 inhibitor mAb316P. The Lp(a) levels thus increased by 5 mg/dL or about 15% over baseline. These data taught the skilled person that Lp(a) levels were not reduced in patients not on statins, but rather were increased.

Claim 1 required an absolute reduction of Lp(a) levels also in patients not on statin treatment It was not sufficient to "reduce the increase of Lp(a)" as argued by the proprietor. The reduction of Lp(a) levels in patients not on statins was thus not sufficiently disclosed in the patent.

Furthermore, a therapeutic effect associated with a reduction of Lp(a) was not made plausible in the patent and many scenarios encompassed by claim 1 were not considered therapeutic in nature.

Inventive step (Article 100(a) EPC and Article 56 EPC)

Document D110 explicitly taught that PCSK9 inhibitors can reduce Lp(a) levels. This was credible *per se* and was supported by evidence in the prior art disclosing the underlying mechanism of action:

- PCSK9 inhibitors acted by upregulating the LDLR
- Lp(a) could be cleared via the LDLR (see post-published document D107 summarising 11 prior art documents and prior art documents D20, D94, D103, D104, D106 and D139)
- statins which act by upregulating the LDLR were also reported to reduce Lp(a) (see documents D20, D61, D62)
- elevated Lp(a) levels in humans with a non-functional LDLR (see documents D20 and D106)
- a genetic study taught the link between PCSK9 and Lp(a) levels (see document D4)

Moreover, document D22 also explicitly stated that PCSK9 inhibitors can decrease Lp(a) levels (see abstract). The "unknown" for the effect of PCSK9 inhibitors on Lp(a) levels in Table 3 of document D22 was further qualified in the text below the table by stating that a decreasing effect was conceivable.
The only difference between the claimed subject-matter and the disclosure in document D22 was that the former included a threshold value of "30 mg/dL" for Lp(a) which, however, was an arbitrarily selected value that could not render the claims inventive.
Moreover, the patient in document D110 was being treated with a statin combined with Ezitimib and was described as having a moderately elevated Lp(a) level. This meant the Lp(a) level must have been at least 30 mg/dL. There was no apparent technical effect associated with this difference. The objective

technical problem solved by the claimed subject-matter was to apply the teaching of document D110 (i.e., lowering Lp(a) using a PCSK9 inhibitor) to further (arbitrarily defined) patients suffering from or at risk of CVD or TOD, i.e. to apply this teaching to "alternative" patients (to the extent that an Lp(a) level of >30 mg/dL was a distinguishing feature at all). The claimed solution was obvious. Electing patients based on an Lp(a) level of >30 mg/dL was not associated with any technical effect, let alone improvement.

Document D3 disclosed antibodies or antigen-binding fragments thereof that specifically bound to human PCSK9 (see page 241, claim 1; title page, abstract; page 1, par. [0006] onwards) as well as the use of these for treating patients with hypercholesterolemia or at risk for developing hypercholesterolemia (see page 5, paragraph [0044]), in particular patients on a therapeutic statin regimen (par. [0043] and [0126]; and claim 23). Claim 1 only required measurement of Lp(a) levels of the patient to be treated and that the anti-PCSK9 antibodies reduced this Lp(a) level. Based on this difference, the technical problem starting from document D3 could be formulated as the provision of a further use for anti-PCSK9 antibodies. The solution of using them to reduce Lp(a) levels was obvious because Lp(a) was routinely measured in hypercholesterolemia patients, including those treated with anti-PCSK9 antibodies (see document D1). Thus, the skilled person following the teaching of document D3 by treating hypercholesterolemia with an anti-PCSK9 antibody would routinely measure Lp(a) levels and thus find the results of the antibody on Lp(a) reported in the examples of the patent.

Moreover, it was already known in the prior art that PCSK9 inhibitors can reduce Lp(a) levels (see documents D22 and D110). Thus, the claimed subject-matter lacked inventive step. The same reasoning applied when starting from documents D1 or D23.

XVII. The patent-proprietor requests that the decision under appeal be set aside and the patent be maintained as granted or alternatively, on the basis of one of the sets of claims of auxiliary requests 1 to 35. It also requests that documents D148 and D153 (renumbered by the Board as document D154) be admitted into the appeal proceedings and that documents D115 and D116 not be admitted into the appeal proceedings.

XVIII. Opponent 1 requests that the decision under appeal be set aside and that the patent be revoked. It also requests that documents D148, D151 (former D148 filed by the patent proprietor), and the declaration labeled D153 (renumbered by the Board as document D154) not be admitted into the appeal proceedings.

Opponent 1 further requests that the arguments of the patent proprietor with regard to the interpretation of values in Table 3B of the patent not be admitted because they represent an amendment of the patent proprietor's case (Article 12(4) RPBA); that auxiliary requests 18 to 21, 23, 25, 27 to 30, 32 and 34 which were not considered in the decision under appeal and only filed with the reply to its appeal, not be admitted into the proceedings; that auxiliary requests 9, 13, 15, 17, 22, 24, 26, 31, 33 and 35 not be admitted into the proceedings because they were filed late and no justification for this late filing was provided; and that documents D115 and D116 be considered, as they were already in the proceedings.

Reasons for the Decision

Admission of documents D115, D116, D148, D151 (former D148), D154 (former D153)

1. As none of these documents is relevant for the decision it was not necessary to decide on their admission.

Main Request (patent as granted)

Claim construction – claim 1

2. Claim 1 is in the format of a purpose-limited product claim under Article 54(5) EPC which reads: "*Paragraphs 2 and 3 shall also not exclude the patentability of any substance or composition referred to in paragraph 4 for any specific use in a method referred to in Article 53(c), provided that such use is not comprised in the state of the art.*"

3. Opponent 1 argued that the claim was not a purpose-limited product claim under Article 54(5) EPC because "*use in reducing lipoprotein(a) (Lp(a)) levels in a patient who exhibits a serum Lp(a) level above 30 mg/dL*" was not limited to therapeutic uses, but included non-therapeutic uses. In support of this argument opponent 1 referred to the lack of a clear causal link between the reduction of Lp(a) and the risk of cardiovascular diseases.

4. Whether the claimed subject-matter is a purpose-limited product under Article 54(5) EPC can be determined by asking if the "specific use" defined in the claim also includes non-therapeutic uses.

5. In the present case the question arises whether reducing Lp(a) levels in a patient who exhibits a certain Lp(a) level falls completely under the exclusion of Article 53(c) EPC or whether it also includes uses which are not methods of treatment of the human body by therapy.

6. The board has seen no evidence that reducing Lp(a) levels in patients exhibiting a serum Lp(a) level above 30 mg/dL could represent a non-therapeutic intervention, e.g. for the purpose of performance enhancement, for cosmetic reasons or for life style improvement etc. The submissions of opponent 1 in this regard (see Annex A to its statement of grounds of appeal) relate instead to whether Lp(a) levels in patients are connected with cardiovascular diseases. However, these considerations are irrelevant for the question whether reducing lipoprotein(a) levels in a patient includes non-therapeutic purposes. The patent proprietor has provided ample evidence that elevated Lp(a) levels were generally considered a health risk at the relevant date of the patent (see review articles D11, D61, D63). Also in the documents cited as closest prior art by opponent 1, e.g. documents D22 and D110, the risk of elevated Lp(a) levels is recognised. It is established case law that "therapy" within the meaning of Article 53(c) EPC is not restricted to curing a disease, but also includes alleviating symptoms and reducing risk of occurrence of disease (see Case Law of the Boards of Appeal, 10th edition 2022, I.B.5.5.2). The board, in view of the common general knowledge in the art as reflected in the cited reviews, considers elevated Lp(a) levels a health risk (see abstracts of documents D11, D61 and D63) and that "*reducing lipoprotein(a) (Lp(a)) levels in a patient exhibiting a serum Lp(a) level above 30 mg/dL*" represents a

treatment by therapy excluded by the provisions of Article 53(c) EPC.

7. Therefore, claim 1 of the main request is to be considered a purpose-limited product claim within the meaning of Article 54(5) EPC.

8. The board agrees with opponent 1 that the definition of a patient "who is diagnosed with or identified as being at risk of developing a cardiovascular disease or disorder prior to or at the time of administration of the composition, or who is diagnosed with or identified as being at risk of developing a thrombotic occlusive disease or disorder prior to or at the time of administration of the composition" does not require that these conditions are treated. Indeed, the claim defines the "use" only as "*reducing Lp(a) levels*" in such a patient. The claim does also not require the reduction of the risk of developing any of the diseases or disorders mentioned.

9. The definition of the patient group by the conditions from which the patient suffers is not limiting because
1) no concrete point in time at which the diagnosis/ identification is made is specified ("*prior to or at the time of administration*", can be any time in the patient's life up-to and including the time of administration)
2) the type of diagnosis/identification is undefined
3) the degree of risk is undefined
4) the type of disorder is defined in such a way as to include a large percentage of the population (*cardiovascular disease or disorder, thrombotic occlusive disease or disorder*).

Novelty (Article 100(a) EPC and Article 54 EPC)

10. The patient group in the claim is further defined as "*exhibiting a serum Lp(a) level above 30 mg/dL*". According to the case law the definition of a new subgroup of patients can establish novelty of a second-medical use claim (see Case Law of the Boards of Appeal, 10th edition 2022, I.C.7.2.4 b)). Opponent 1 has not cited any prior art disclosing treatment of a patient having a serum Lp(a) level above 30 mg/dL with an anti-PCSK9 antibody.

11. In the present case, the Lp(a) level of at least 30 mg/dL is a clear and measurable physiological parameter which is functionally related to the pathological status of the patient (see point 6. above).

12. In the context of inventive step, opponent 1 argued that the threshold of 30 mg/dL was arbitrarily selected. The board agrees that there is a certain degree of arbitrariness in parameters for medical treatment. As it is put in the expert declaration D64:

> "*These types of thresholds are effectively guidelines, set by clinicians, to provide a simple framework for deciding when to give treatment and when not to treat. However, these thresholds are somewhat arbitrary, and based on a risk/benefit (and sometimes cost/benefit) analysis*".

13. These considerations do not mean that the threshold is not meaningful and purposive in the sense of the established case law on novelty of further medical use claims conferred by the selection of a patient group. This is confirmed by the statement in document D64 that

"*epidemiological studies provided a clear indication that risk of cardiovascular disease was elevated in patients with a plasma Lp(a) level above 30 mg/dL [...] giving a clear scientific rationale for Lp(a)-lowering therapy in such patients. Accordingly, 30 mg/dL is an appropriate threshold for defining the patients to be treated for Lp(a) lowering in the claims*".

14. Thus, the choice of the patient group having Lp(a) levels of at least 30 mg/dL, as defined in the claim, is not arbitrary.

15. Reducing lipoprotein(a) (Lp(a)) levels by using anti-PCSK9 antibodies in a patient exhibiting a serum Lp(a) level above 30 mg/dL is not disclosed in the cited prior art, e.g. documents D3 or D23. In particular, none of these documents discloses a reduction of Lp(a) levels nor a patient group having Lp(a) levels of at least 30 mg/dL.

16. These features of claim 1 are also not disclosed in documents D115 and D116, the admission of which was contested by the patent proprietor. Even taking into account those documents, the board's finding on novelty would therefore not change.

17. In view of this, it is not necessary to determine whether reducing Lp(a) levels represents a new clinical situation, as suggested by opponent 1.

18. The subject-matter of claim 1 is novel (Article 54 EPC). The same applies to the subject-matter of dependent claims 2 to 12 which share all features of claim 1.

Admission of new arguments by the patent proprietor (12(4) RPBA)

19. Opponent 1 requested that the patent proprietor's arguments concerning Table 3B in the patent (see reply to the patent proprietor's statement of grounds of appeal, page 2, point 5) not be admitted into the proceedings. The patent proprietor had submitted a series of calculations based upon median percentage lowering over baseline Lp(a) levels and purported common general knowledge about Lp(a) for the first time in appeal. In opponent 1's view, these arguments were an amendment to the patent proprietor's case which was also complex in view of the necessary calculations.

20. The patent proprietor argued that the opposition division, during oral proceedings, had focused on the median values in Table 3B and, based on a wrong interpretation of these values, had come to the conclusion that the invention lacked sufficient disclosure. This had been surprising to the patent proprietor at the time and it had not had time to react appropriately during the oral proceedings. Therefore the respective arguments could only be filed with the statement of grounds of appeal.

21. The opposition division's preliminary opinion set out in its communication dated 5 July 2021 (see sheets 6 and 7), the minutes of the oral proceedings before the opposition division (see sheets 3 and 4) and the decision under appeal (see point 13.2.2) all corroborate the explanation provided by the patent proprietor.

22. According to Article 12(4) RPBA with regard to amendments to a party's case the board shall exercise

its discretion in view of, *inter alia*, the complexity of the amendment, the suitability of the amendment to address the issues which led to the decision under appeal, and the need for procedural economy.

23. The board considers that the patent proprietor's new arguments are straight forward and are based on the common general knowledge of the skilled person for interpreting scientific data. Moreover, they address the issue of sufficiency of disclosure which led to the decision under appeal. They are also not detrimental to procedural economy because they do not introduce new facts, but only interpret the data in the patent. Finally, these arguments represent a timely reaction to the assessment made at the oral proceedings by the opposition division. The patent proprietor could not, at the oral hearing, be expected to respond with calculations and to explain in a substantiated way why the median value in a given group of Table 3B could not be indicative of the overall lowering of Lp(a) and why the opposition division's finding that the patent did not demonstrate Lp(a) lowering from baseline in non-statin-treated patients was wrong in fact. In view of these circumstances, the board admitted the arguments with regard to Table 3B into the appeal proceedings.

Disclosure of the invention(Article 100(b) EPC)
Therapeutic effect of reducing Lp(a) levels

24. In line with the claim construction by the board (see points 6. to 8. above), the objections brought forward by opponent 1 in relation to a missing link between Lp(a) levels and a preventive or therapeutic effect of CVD or TOD, play no role in the assessment of sufficiency of disclosure. The only effect that is a feature of the claim is the reduction of Lp(a) levels

in a patient who exhibits a serum Lp(a) level above 30 mg/dL. No evidence was provided that this cannot be achieved.

Effect without statins

25. In its decision, the opposition division held that the invention to which claim 1 related was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art because "*Table 3B show* [sic] *that without statins, Lp(a) levels increase compared to baseline, both in patients receiving placebo and in patients receiving the PCSK9 inhibitor*" (see point 13.2.2). Since there was no working example in the patent showing a lowering effect of Lp(a) in patients who do not receive statins it was also not possible to rely on evidence published after the filing date.

26. However, the opposition division appears to have misinterpreted the data in Table 3B. This table reports data from patients with "*Diet Only - No Atorvastatin Treatment*", i.e. patients who are not treated with statins. It compares a group of 2 patients (N=2) treated with placebo (Pbo) with a group of 8 patients (N=8) treated with 150 mg mAb316P (anti-PCSK9 antibody). In the last four rows of the column relating to Lipoprotein(a) it shows the median and the minimum and maximum Lp(a) levels in mg/dL at baseline and at day 57 for both patient groups. It was common general knowledge that the median refers to the value in a group of values which has the same number of values above and below it. In the case of even numbers of values (here 2 and 8) the median is calculated as the average of the two middle values (i.e. the average of the 1st and 2nd value in the case of placebo and the

average of the 4th and the 5th value in the case of mAb316P). The median is not to be confused with the mean or average of all values. The skilled person would understand that in the case of the patient group treated with antibody only, the median value and the values of the patients with the lowest (min) and the highest (max) values are provided, but that the values for the other six patients are not reported. It is also common general knowledge that an increase in the median does not necessarily equate to an increase in the average or mean of the values. The skilled person would thus realise that the slight increase in the median value does not mean that in the six patients not reported, there had necessarily also been an increase in the Lp(a) level between baseline and day 57.

27. A decrease in the compounded Lp(a) levels in the antibody treated group is provided in the table by the value "% change vs Pbo" which is -43.8%. This negative change is not outweighed by the positive % change in the placebo group (change for first patient: 58-47=11, i.e. 19%; change for second patient: 75-63=12, i.e. 37% change; median change: 28%). It is therefore apparent that the overall Lp(a) levels in the antibody only group must have decreased. The only possible explanation for this reduction that the skilled person could draw from the data in Table 3B is that at least some of the six (unreported) patients had a decrease in their Lp(a) levels that led to the reported overall decrease vs placebo. This is confirmed in the patent in paragraphs [0076] and [0081] which equally state that Lp(a) was lowered in patients "*on diet alone*" and also by the patent proprietor's expert in points 10 and 27 of document D64.

28. Based on the data in the patent alone the board considers it credible that a reduction of Lp(a) levels is also achieved in patients treated with an anti-PCSK9 antibody in the absence of statins. This is not contradicted by later published data in document D2 and associated document D2a (see table S10 and figure S8C).

29. The invention to which the claims relate is therefore sufficiently disclosed (Article 100(b) EPC).

Inventive step (Article 100(a) EPC and Article 56 EPC)
Documents D110 or D22 as starting points

30. Document D110 has been chosen by the parties and the opposition division as representing the closest prior art for the subject-matter of claim 1.

31. Document D110 is a short article in a journal addressed to medical practitioners in which an expert in the field of cardiovascular diseases, Prof. K. Parhofer, replies to the question of a physician whether there exist "*ways of reducing permanently elevated Lp(a)*" (see document D110b, English translation of D110). Document D110 states that "[s]*everal of the new lipid-lowering drugs in development (mipomersen, eprotirome, PCSK9-inhibitors, CETP inhibitors, etc.) can lower lipoprotein(a) levels. It is unclear whether and when these drugs will be approved. Likewise unclear is whether therapy with these drugs brings any clinical benefit*". From this statement, which is the only reference to PCSK9 inhibitors in document D110, it is unclear whether all of the compounds listed are capable of reducing ("*can lower*") lipoprotein(a) levels or only some of them. As argued by the patent proprietor, the wording "*several of*" and the open list ending with "*etc.*" could point the skilled person to the latter

interpretation. However, the fact that PCSK9 inhibitors are listed in response to the question posed to the expert at the outset, could, however, also point in the other direction, i.e. that all listed new lipid-lowering drugs including PCSK9 inhibitors are also potential Lp(a) lowering drugs. Document D110 therefore does not clearly and unambiguously disclose an Lp(a) lowering effect of PCSK9 inhibitors.

32. The patent proprietor furthermore refers to document D22, also by the author of document D110, which in Table 3 discloses that the effect of PCSK9 inhibitors on Lp(a) levels was unknown. Opponent 1 refers in the same document to the abstract which states that "*some medications in development (mimopersen, eprotirome, Propotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, Cholesterol-ester-transfer protein (CETP-inhibitors) can decrease elevated lipoprotein(a) concentration*". In the view of the board, the sentence in the abstract of document D22, similar to the sentence in document D110 cited above, leaves it open whether all medications in the list or only some of them can decrease elevated lipoprotein(a) concentration. Document D22 concludes that "*it is conceivable that PCSK-9 inhibitors, which are currently developed for the treatment of hyperlipidemia may also decrease lipoprotein(a) concentration*" (page 874, left-hand column).

33. Neither document D110 nor document D22 shows, e.g. in the form of experimental data, results of clinical trials or a reference to such data, an effect of PCSK9 inhibitors on Lp(a) levels. The wording of both documents in this regard is ambiguous or even contradictory (compare the Abstract and Table 3 of document D22). The board therefore concludes that

neither document D22 nor document D110 contain a direct and unambiguous disclosure of an effect of PCSK9 inhibitors on Lp(a) levels. At most they contain a suggestion that this might be the case, as in the statement in document D22 introduced with "*it is conceivable*".

34. Document D22 was published in a scientific journal and contains data (see Table 3). It specifies the PCSK9 inhibitor as a PCSK9 antibody (see Table 3) and thus discloses a further feature of claim 1. Document D22 is therefore a more promising springboard for analysing inventive step then document D110. The difference between the claimed subject-matter and the disclosure of document D22 is that the PCSK9 antibody achieves the therapeutic effect of reducing lipoprotein(a) levels in patients. The objective technical problem can be formulated as providing a compound that effectively reduces lipoprotein(a) levels in patients with elevated Lp(a) levels.

35. To decide whether the solution to this problem was obvious it has to be asked whether the statement in document D22 that it was "*conceivable*" that PCSK9 inhibitors could decrease Lp(a) levels would have led the skilled person to test this hypothesis with a reasonable expectation of success (see Case Law of the Boards of Appeal, 10th edition 2022, I.D.7.1). In this regard, the common general knowledge of the skilled person and potential positive or negative indicators in the prior art for the expected success at the relevant date as well as potential difficulties and hurdles when setting out to test the hypothesis are relevant.

36. It is undisputed that it was known that anti-PCSK9 antibodies increase the recycling of LDL-receptor (LDL-

R) by binding to their target, PCSK9, which causes an increase of the density of LDL-R on the cell surface. This, in turn, decreases LDL-C which is cleared by LDL-R.

37. The patent proprietor pointed to a number of documents which shed doubts on a similar link between anti-PCSK9 antibodies, LDL-R levels and Lp(a) levels. Document D63, a review article published in 2010, i.e. about a year before the priority date of the patent, states that

"*Metabolic pathways for in vivo Lp(a) catabolism are not totally clarified. Catabolism occurs primarily in the liver but mechanisms involved are not well known.[32,33] LDL receptor does not seem to have a crucial role in Lp(a) metabolism. This affirmation is based on the fact that statin administration (which causes LDL receptor upregulation) does not affect significantly Lp(a) plasma concentration.[27] Likewise, studies in mice have shown that the LDL receptor, apoE, and the asialoglycoprotein receptor do not participate significantly in Lp(a) catabolism.[32,34]*" (see page 264, right-hand column, last paragraph).

Also document D62, a review article published in October 2010, states that "[i]*t is believed that plasma concentrations of Lp(a) are determined chiefly by rates of hepatic synthesis of apolipoprotein(a)*" and that "[l]*ipoprotein(a) is thought to be catabolized primarily by hepatic and renal pathways, but these metabolic routes do not appear to govern plasma Lp(a) levels*" (see page 2849, right hand-column, first full paragraph). Further, the review article D61, published in 2011, states that "*evidence of a beneficial clinical effect of statins in the presence of elevation of*

plasma Lp/a) levels is still limited and heterogeneous" (see page 2, right-hand column, second paragraph) and the review article D11, also published in 2011, points out that "*some studies even showed an increase in Lp(a) concentrations in response to statin treatment*" while it was known that "*statins work by upregulating LDL receptor*" (page 686, left-hand column, under the heading "*Statins*"). None of these scientific reviews mentions PCSK9 inhibitors as potential candidates for reducing Lp(a) levels.

38. Opponent 1 referred to other passages in the documents cited by the patent proprietor (D11, D61, D62) and to further documents (D20, D94, D103, D104, D106) to argue that at least a small reduction of Lp(a) through the known LDL-R increasing effect of PCSK9 antibodies was to be expected by the skilled person.

39. In particular, opponent 1 referred to document D11 which states that "*there are 2 possible mechanisms for the statin-associated small Lp(a)-lowering effect. First, there is some evidence suggesting that Lp(a) is partially removed from the circulation via the LDL receptor [78], although the LDL receptor does not seem to play a major role in Lp(a) clearance [79]. Second, approximately 10-25% of Lp(a) is converted to LDL when apo(a) is cleaved off and LDL is then cleared by the LDL receptor.*" (see page 686, left-hand column, second full paragraph) and that "[t]*he mechanism through which eprotirome decreases Lp(a) concentrations may be the upregulation of the LDL receptor*" (see page 687, right-hand column, penultimate paragraph). This showed that two other compounds which decreased Lp(a) levels (statins and eprotirome) acted through upregulation of LDL-R, similar to PCSK9 inhibitors. Also documents D20, D94, D103, D104, D106 supported the clearance of Lp(a)

through LDLR, e.g. D20, title: "Long term statin treatment reduces lipoprotein(a)"; D94, Abstract: "*Lp(a) is specifically bound with high affinity to the same receptors of human fibroblasts as LDL*"; D103, Abstract: "*this receptor* [LDL-R] *has the potential to play a major role in clearance of Lp(a) from the circulation of intact humans*"; D104, title: "*Defects in the low density lipoprotein receptor gene affect lipoprotein (a) levels*"; D106, abstract: "*mutations in the LDL-R demonstrate a clear gene dosage effect on Lp(a) plasma concentrations*").

40. In response, the patent proprietor noted that several of the reports cited by opponent 1 had been published many years before the priority date of the patent (i.e. D20: 2003, D94: 1983; D103: 1990, D104: 1989, D106: 2000) and had been superseded by newer teaching such as that in documents D61, D62 and D63 (see point 37. above). Also the review D11, albeit finding some evidence for involvement of LDL-R in removing Lp(a) from the circulation cautioned that "*the LDL receptor does not seem to play a major role in Lp(a) clearance [79]*" (see page 686, left-hand column, second full paragraph).

41. Opponent 1 further cited document D4 which, in its opinion, showed a genetic link between a PCSK9 genetic variant and increased Lp(a) levels (see page 5, second paragraph, and Table 4). The board agrees with the patent proprietor that these data are not significant because no gene-dosing effect between the heterozygous and the homozygous mutation was observed and the p-value was rather high (0.051). Moreover and importantly, a possible link between a genetic mutation PCSK9 and the level of Lp(a) is no evidence for the

potential Lp(a) decreasing effect of an anti-PCSK9 antibody.

42. Having considered and weighed the evidence brought forward by the parties, the board is persuaded that no clear picture of how Lp(a) levels are regulated in the body and whether LDL-R played a role in this emerges from the skilled person's the common general knowledge at the relevant date of the patent. This is reflected in the review articles published shortly before the priority date. Apart from the isolated suggestions in documents D110 and D22 - which are unsupported by any data and were both authored by the same person - no suggestion in the prior art to use PCSK9 inhibitors has been brought forward. The skilled person would therefore have considered the suggestion in document D22 ("*it is conceivable*") with care and would have had no reasonable expectation that PCSK9 antibodies could reduce Lp(a) levels in patients.

43. In view of the unclear picture with regard to the metabolism and catabolism of Lp(a) in humans and the lack of clear evidence for an involvement of LDL-R, the board concludes that the skilled person at the relevant date of the patent would have had no reasonable expectation of success that PCSK-9 inhibitors would decrease Lp(a) levels in patients.

44. Moreover, as submitted by the patent proprietor and not contested by opponent 1, at the priority date, anti-PCSK9 antibodies had been tested in patients in a phase 1 clinical trial (see document D1) and a phase 2 clinical trial had just started (see document D23). Regulatory approval for clinical use did not follow until 2015. Testing the effect of anti-PCSK9 antibodies on Lp(a) levels in patients, would have required a new

clinical study in humans. Since many model animals do not express Lp(a) (see document D133, page 760, first paragraph) it would not have been straightforward to carry out such a a test in animals. Opponent 1 referred to mouse models, but as noted by the patent proprietor, expression of human apo(a) in mice does not lead to Lp(a) in the plasma of the animals because mouse apoB does not form a complex with human apo(a) (see document D133, *ibid.*). In the absence of encouraging data in the prior art, the board considers that the use of cynomologus monkeys as models (as in document D3, Example 13) would have been difficult due to the extended ethical review that would have been required before embarking on such work. It is established case law that in such a case the skilled person would usually not adopt a "try and see" attitude, but would need to have a reasonable expectation of success (Case Law of the Boards of Appeal, 10th edition 2022, I.D. 7.2, citing decisions T 293/07, T 847/07, T 1545/08 and T 1011/17).

45. Since there is also no other prior art document which suggests using anti-PCSK9 inhibitors to lower Lp(a) levels, the claimed subject-matter is inventive (Article 56 EPC).

Documents D1, D3 or D23 as starting points

46. This conclusion on inventive step is not changed when starting from the disclosure of documents D1, D3 and D23, as suggested by opponent 1. Indeed, none of these documents discloses an effect of PCSK9 inhibitors on Lp(a) levels.

47. Document D1 relates to a phase 1 clinical trial of PCSK9 inhibitors. It reports dose-dependent reductions

of LDL-C, no change of HDL-C and no dose-limiting toxicity. Lp(a) is mentioned as one of the pharmacodynamic parameters measured, but no results are reported in this regard. Documents D3 and D23 do not mention Lp(a).

48. Opponent 1 argued that starting from document D3, the objective technical problem could be formulated as providing a new use for PCSK9 inhibitors and that merely by repeating the teaching of document D3 (or D1 or D23) which routinely involved measurement of Lp(a) levels the skilled person would have arrived at the subject-matter claimed.

49. The board does not agree with this conclusion. The skilled person, starting from the disclosure in document D3 and seeking a solution to the above formulated problem, would not have found any indication in that document that PCSK9 inhibitors could lower Lp(a) levels, even taking into account common general knowledge or other disclosures in prior art documents (see points 37. to 41. above). From the disclosure in document D1, which is the only document that mentions Lp(a), the skilled person could have concluded that Lp(a) was one of seven pharmacodynamic parameters measured. An effect of the anti-PCSK9 antibody on other parameters than LDL-C (reduced) and HDL-C (no change) is not reported. Even when setting out to find new uses for PCSK9 inhibitors, as suggested by opponent 1, the skilled person would have had no reasonable expectation that Lp(a) levels would be reduced by PCSK-9 inhibitors or that lowering Lp(a) levels would be beneficial for a particular patient group. Since in document D1 the patients were selected for their LDL-C>100 mg/dL and fasting triglycerides <=200 mg/dL levels, determining if anti-PCSK9 inhibitors lowered Lp(a) levels would

have required running a new clinical trial with the appropriate patient groups and controls. Nothing in document D1 or in the remaining prior art suggests to embarking on such a research project. As established in point 44. above, the skilled person was also not in a "try and see" situation.

50. The board concludes that also when starting from documents D1, D3 or D23, the skilled person would not have arrived at the claimed subject-matter.

51. The subject-matter of claim 1 is inventive (Article 56 EPC). The same applies to the subject-matter of dependent claims 2 to 12 which share all features of claim 1.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

1. The patent is maintained as granted.

The Registrar: The Chairman:

I. Aperribay A. Chakravarty

Decision electronically authenticated