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Datasheet for the decision of 16 April 2013

Case Number: T 1439/09 - 3.3.08

Application Number: 99963986.7

Publication Number: 1133558

IPC: C07K 14/51, C07K 16/22, A61K 39/395

Language of the proceedings: EN

Title of invention:
Compositions and methods for increasing bone mineralization

Patent Proprietor:
UCB Pharma S.A.

Opponent:
ELI LILLY AND COMPANY

Headword:
Sclerostin/UCB PHARMA

Relevant legal provisions:
EPC Art. 83, 54, 56, 111(1)
RPBA Art. 13(3)

Keyword:
"Anonymous third party observations (deemed not to have been filed (see points 1.7, 1.8))"
"Sufficiency of disclosure (yes), novelty (yes), inventive step (yes)"

Decisions cited:
T 0367/96, T 0609/02, T 0146/07

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1439/09 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 16 April 2013

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 19 May 2009 concerning maintenance of European patent No. 1133558 in amended form.

Composition of the Board:

Chairman: M. Wieser
Members: B. Stolz
J. Geschwind

Summary of Facts and Submissions

I. The appeal lies against the interlocutory decision to maintain European patent No. 1133558 on the basis of auxiliary request I filed on 22 January 2009. The opposition division found that the main request before it did not meet the requirements of Article 54 EPC.

II. With its grounds of appeal, filed on 30 September 2009, the opponent (appellant) submitted new documents D49 to D56.

III. With its response, filed on 15 April 2010, the patentee (respondent) submitted new documents D57 to D64.

IV. In a further submission, filed on 18 March 2011, the appellant submitted new documents D65 to D73 and additional arguments.

V. With letter dated 21 July 2011, the respondent requested separate oral proceedings to clarify procedural issues before oral proceedings on the substantive issues were held.

VI. Anonymous third party observations were filed on 12 September 2011.

VII. In a notice dated 14 October 2011, the board informed the parties about the third party observations and drew their attention to Articles 12 and 13 of the Rules of Procedure of the Board's of Appeal (RPBA).

VIII. Both parties filed comments on the third party observations. In response to appellant's submissions of

18 March 2011, the respondent filed a new main request and auxiliary requests I to XIII.

IX. In a communication pursuant to Article 15(1) RPBA, annexed to the summons to oral proceedings, to be held on 16 April 2013, the board informed of its preliminary, non-binding opinion on some of the issues to be discussed at the upcoming oral proceedings.

X. In a letter dated 20 February 2013, the appellant introduced a new novelty objection based on a divisional application of the opposed patent.

XI. With its final written submissions before oral proceedings, dated 15 March 2013, the respondent filed new documents D74 to D77, D78a to D78z, D79 to D93, a new main request and auxiliary requests I to XXIX.

XII. With its final written submissions before oral proceedings, the appellant submitted new documents D100 to D103.

XIII. Oral proceedings were held on 16 April 2013. During the proceedings, the respondent filed a new main request which is identical with auxiliary request II filed on 15 March 2013.

XIV. Independent claims 1, 19, 20 and 25 of the main request read:

"1. An isolated nucleic acid molecule comprising sequence ID No. 1, 5, 9, 11, 13 or 15, or complementary sequence thereof.

19. An isolated protein comprising a TGF-beta binding protein of SEQ ID NO: 2, 6, 10, 12, 14 or 16.

20. A monoclonal antibody or fragment thereof that binds to a TGF-beta binding protein encoded by a nucleic acid molecule of Sequence ID No. 1, 5, 9, 11, 13, or 15 with a Ka of greater than or equal to 10^8 M^{-1} and does not bind the protein Dan or the protein Gremlin.

25. Use of an antibody or antibody fragment according to any one of claims 20 to 24 in the manufacture of a medicament for increasing bone mineralization in a warm-blooded animal."

XV. The following documents are cited in this decision:

D3: Van Hul et al., 1998, Am. J. Hum. Genet. 2:391 - 399

D22: Staehling-Hampton et al., 2002, American Journal of Medical Genetics 110: 144-152

D33: Kusu et al., 2003, The Journal of Biological Chemistry 278(26): 24113-24117

D38: Brunkow et al., 2001, Am J. Hum. Genet. 68: 577-589

D42: Van Bezooijen et al., 2007, J. Bone Min. Res. 22: 19-28

D48: WO 2008/1152732 (Eli Lilly and Company)

D51: Declaration of Dr. Edgar Wingender

D55: Declaration of Dr. Auristela Freire

D58: WO 2009/047356 of Novartis AG

D59: Second Declaration of Dr. Martyn Robinson

D61: Declaration of Professor Timothy Arnett, 2 April 2010

D65: WO 00/75317 (Genentech, Inc.)

D70: US provisional application 60/151,700 filed on August 31, 1999

D86: Krause et al., 2010, The J. Biol. Chem. 285(53): 41614-41626

D90: Alberts et al., 1994, Molecular Biology of the Cell, 3rd ed., Garland Publ. Inc., p. 1212

D101: Wollenberger, Rennebarg, Bier & Scheller, 2003, Analytische Biochemie, Wiley VCH, pp. 47-49

D102: Abbas, Lichtman & Pober, 1997, Cellular and Molecular Immunology, 3rd ed., W.B. Saunders Co., p. 54

D103: Chmiel ed., 2011, Bioprozesstechnik, 3rd ed., Spektrum Akad. Verlag, p. 31

XVI. The arguments of the appellant, as far as relevant for the present decision, can be summarized as follows:

Admission of late filed arguments, documents and requests:

The main request and auxiliary requests I to XXIX were only filed with letter of 15 March 2013 and should therefore not be admitted.

Rule 81(1) EPC stated that "Grounds for opposition not invoked by the opponent [with its statement under Rule 76(2)(c)] may be examined by the Opposition Division of its own motion if they would prejudice the maintenance of the European patent". The opposition division based its decision on the admissibility of the late filed grounds of opposition however on the degree of relevance of the objections. It did not ask if the grounds for opposition, i.e. inadmissible amendments and lack of industrial applicability, prejudiced the maintenance of the European patent (grounds for the decision, page 4, lines 5 to 7) and therefore did not exercise its discretion correctly.

The anonymous third party observations were highly relevant and should therefore be admitted.

Claim 20, directed to antibodies, lacked novelty over the divisional European patent application No. 06011535 under Article 54(3) EPC. This was due to the fact that the claim did not enjoy a right to priority, whereas the divisional application disclosed an antibody embodiment that was more specific and enjoyed the right to priority. Under these circumstances, the divisional application, upon its publication, anticipated the

subject matter of claim 20 (Article 54(3) EPC). This objection was highly relevant and it was raised as soon as the appellant became aware of it. Since the divisional application was based on the application documents of the patent under appeal, the respondent could not be surprised by its content. The admission of this new argument would not lead to any delay of the appeal procedure.

Document D65 and the corresponding priority document D70 were highly relevant because they anticipated the subject matter of claim 20 under the provisions of Article 54(3) EPC.

Article 83 EPC

Claim 25 and the claims dependent on it related to the use of antibodies against Sclerostin in the manufacture of a medicament, subject matter which was insufficiently disclosed. The patent itself did not disclose any antibody suitable for treating a disease of bone deficiency. Furthermore, Document D86 showed that the Sclerostin/BMP (bone morphogenic protein) interaction occurred intracellularly whereas the extracellular interaction between the two was not relevant. Since an antibody administered to a patient could not enter its cells, no inhibition of BMP binding to Sclerostin could be achieved. Since the patent taught the screening of compounds for an effect on the BMP/Sclerostin interaction in order to find medically useful candidate molecules, the skilled person had no means to identify antibodies that would increase bone mineral content. The situation might have been different if the Patent had actually made accessible

active inhibitors, as judged from in vivo functional inhibition of Sclerostin, or if the patent had identified regions of Sclerostin important for its in vivo functions. Under such circumstances, the mode of action might not have mattered. The skilled person, left with the teaching of the patent was however led in the wrong direction. Antibodies resulting from the screening for inhibitors of the Sclerostin/BMP interaction would not inhibit the extracellular interaction of Sclerostin with Wnt and the LRP5/6 receptors. Animal models of bone formation were not suitable for the screening of large numbers of antibodies for ethical reasons, and cell based in vitro assays were unreliable and allowed no conclusion about in vivo efficacy.

Article 54(3) EPC

Document D65 and the corresponding priority document disclosed monoclonal antibodies specifically recognizing protein PRO7476 which was identical with Sclerostin encoded by Seq ID 1. Antibodies with high specificity for a protein could be expected to bind with a Ka of at least 10^8 M^{-1}. Document D101 disclosed a value of 10^8 M^{-1} as a typical mean value for Ka. Documents D101 and D102 also mentioned typical ranges of Ka values from 10^4 to 10^{12} M^{-1}. It was therefore clear that a substantial fraction or the majority of any monoclonal antibodies recognizing PRO7476/Sclerostin had a Ka value according to the claim.

Article 56 EPC

The goal of finding a potential target for treating bone growth diseases was not new, and the gene sequence encoding Sclerostin could be easily identified in databases by applying standard in silico techniques. Document D3 disclosed the concept of using a bone growth disease gene as a therapeutic target for the treatment of diseases with low bone density. It disclosed a candidate chromosomal region for a gene related to Van Buchem disease on chromosome 17 and pointed to a well known link between Van Buchem disease and sclerosteosis. This would have prompted the skilled person to test and compare possible candidate sequences. As shown in the expert declaration of Prof. Wingender (document D51), at the time of filing, the skilled person would have applied standard computer skills to search the chromosomal region mentioned in document D3 for genes with homology to bone related proteins. Using the ENTREZ system of NCBI and on the basis of the existing markers, this would have led the skilled person to a limited number of 17 sequenced clones. Only 5 of these could have been relevant, the others were either too small or known to encode unrelated genes. The 5 clones bore 27 predicted peptide sequences, 19 of which had homologies to proteins which were unrelated with bone formation. One of the proteins was the most likely candidate because it had homology to DAN, a protein known to belong to a family of proteins inhibiting the function of BMPs. The skilled person would then have checked an EST database and performed standard wet lab assays with the candidate gene. In addition, the skilled person would have searched for aberrant features in this putative disease gene in Sclerosteosis patients. Samples from patients were available as declared in document D55. Thus, starting

from document D3 as the closest prior art, no inventive skills were needed to arrive at the claimed solution in an obvious way.

XVII. The arguments of the respondent, as far as relevant for the present decision, can be summarized as follows:

Admission of late filed arguments, documents and requests:

The main request and auxiliary requests I to XXIX were filed in response to the late introduction of documents D65 and D70 and should therefore be admitted.

The opposition division refused to admit the late filed objections under Article 123(2) EPC and Article 57 EPC because it considered them not to be prima facie relevant and not to prejudice the maintenance of the patent. There was thus no reason to admit them into the appeal proceedings.

The third party observations were late filed, unsigned and anonymous. As a matter of principle, such observations should not be regarded in opposition or appeal proceedings. The third party observations addressed issues which the opposition had refused to admit into opposition proceedings. Admitting them now would render ineffective the procedure before the first instance and the procedure before the board of appeal and create the possibility of an abuse of the appeal procedure.

The objection of lack of novelty over the divisional application was late filed, and the issue raised highly complex legal questions as to whether a divisional

application can be cited against its parent application. Should the board admit this objection, questions of law would have to be referred to the Enlarged Board of Appeal.

The late filed prior art documents D65 and D70 should not be admitted because the objections raised by the appellant were not relevant. Admitting them would create a fresh case which would run contrary to the principle that an appeal procedure was primarily a review of the correctness of the decision taken at first instance.

Article 83 EPC

The claims directed to the medical use of antibodies raised against Sclerostin required that the antibody was able to increase bone mineralisation in a warm-blooded animal. The molecular mechanism by which this happened was not mentioned in the claim. The teaching of the patent was not limited to the identification of inhibitors of the Sclerostin/BMP interaction but, as disclosed in paragraph [0030] of the specification, also included determining whether a candidate molecule altered the signalling of TGF-beta family members such as BMP 5 or 6. Moreover, as stated e.g. in one of the appellant's expert declarations (document D51, Annex EW6), cell based assays for bone formation were known and could be routinely applied. If they could be used to screen for Sclerostin function, they could also be used to screen for antibodies antagonizing the effect of Sclerostin. Apart from this, post published document D86 confirmed that Sclerostin indeed interacted with BMPs.

Article 54(3) EPC

Highly specific monoclonal antibodies were not the same as monoclonal antibodies with a certain minimal affinity for a target epitope. As shown in document D90, Ka values of monoclonal antibodies ranged from $5x10^4$ to 10^{11} M^{-1}. Document D65 did not mention Ka values at all. Therefore, it did not disclose the subset of antibodies with a Ka of equal to or greater than 10^8 M^{-1}.

Article 56 EPC

Document D3 mapped a mutation associated with overproduction of bone in Van Buchem Disease to a candidate region of about 0.7 cM on chromosome 17. A person interested in identifying a gene involved in the regulation of bone production could have tried to identify a polymorphism in an affected gene. This would however not have led to the identification of Sclerostin because patients with Van Buchem Disease carry mutations in regulatory sequences but not in the sequence encoding Sclerostin. A pure in silico approach, as submitted by the appellant, would not have led to the claimed invention in an obvious way either. The vast majority of the candidate region in document D3, including the regulatory sequence later found to carry the mutation in Van Buchem Disease, had not been sequenced before the priority date and could not be analysed. It was not obvious that the gene encoding Sclerostin lay in the small sequenced fraction. There was a large number of genes in the sequenced candidate region whose putative functions suggested a role in bone growth and it was not obvious to pick out

sclerostin. Since it was not obvious that the mutation in Van Buchem Disease caused a total loss of function, appellant's argument, that the skilled person would have discarded many genes on the basis that either a total loss of function would have been incompatible with the phenotype of the disease or a developmental phenotype would have been expected, was not tenable. The appellant's approach presupposed that the skilled person would have taken multiple decisions in the right direction along the path to the invention. This clearly implied hindsight.

XVIII. The appellant requested that the decision under appeal be set aside and the patent be revoked.

XIX. The respondent requested that the appeal be set aside and the case be remitted to the first instance with the order to maintain the patent on the basis of claims 1 to 41 of the main request filed at the oral proceedings before the board.

Reasons for the decision

1. Procedural requests

Late filed grounds of opposition

1.1 The appellant submitted that the opposition division erred in the exercise of its discretion when it decided not to admit the late filed grounds of opposition of Article 100(a) EPC in combination with Article 57 EPC, and of Article 100(c) EPC into the proceedings. Referring to Rule 81(1) EPC, it was of the opinion that

the rule's language obliged the opposition division to admit new grounds of opposition in any case if they prejudiced the maintenance of the European patent.

1.2 The wording of Rule 81(1) EPC, "Grounds for opposition ... may be examined by the opposition division ..." makes it clear that the opposition division has the discretionary power to admit grounds for opposition which were originally not invoked.

1.3 If the way in which the department of first instance has exercised its discretion on a procedural matter is challenged in an appeal, it is not the function of the board of appeal to review all the facts and circumstances of the case as if it were in the place of the department of first instance, and to decide whether or not it would have exercised such discretion in the same way as the department of first instance. A board of appeal should only overrule the way in which a department of first instance has exercised its discretion if the board concludes it has done so according to the wrong principles, or without taking into account the right principles, or in an unreasonable way (cf. Case law of the Board's of Appeal, 6th edition, VII.E.6.6, and decision cited therein).

1.4 The opposition division held that both grounds were not prima facie relevant, decided not to admit them, and gave an, albeit short, reasoning in its decision.

1.5 Thus, the board comes to the conclusion that the opposition division applied its discretionary power correctly and sees no reason to overturn its decision.

Third party observations

1.6 Anonymous, unsigned third party observations were filed during the appeal proceedings.

1.7 In decision T 146/09, this board, in a different composition, held that the identification of a third party in the context of third party submissions in opposition proceedings was particularly important in order to allow the competent organ of the EPO to verify whether the observations were indeed filed by a third party rather than by a party to the proceedings. Otherwise, a party might be tempted to submit late observations and/or documents by means of anonymous third party observations in order to avoid negative procedural consequences such as apportionment of costs. Moreover, unsigned submissions by a party to the proceedings were deemed not to have been filed if, after a communication according to Rule 50(3) EPC has been sent out by the EPO, they are not signed in due time. Since unsigned anonymous third party observations did not allow the EPO to send out such an invitation, they necessarily remained unsigned. As a consequence, they were deemed not to have been filed.

1.8 In the present case, the board sees no need to depart from this line of reasoning. Therefore, the anonymous observations filed under Article 115 EPC are deemed not to have been filed and are disregarded by the board.

New objection of lack of novelty over a divisional application

1.9 Claim 20 encompasses monoclonal antibodies binding to the protein encoded by any of the recited Seq IDs with a Ka of greater than or equal to 10^8 M^{-1} but not to the protein Dan or the protein Gremlin.

1.10 The appellant submitted that the priority document of the case under appeal did not disclose this subject matter. Thus, the relevant date for the assessment of novelty was the filing date of the patent application.

The appellant further submitted that the divisional European patent application, EP No. 06011535, arising from the patent under appeal, disclosed antibodies falling within the scope of claim 20. In addition, the antibodies according to the divisional application were disclosed in the common priority document. Under these circumstances, claim 20 lacked novelty according to Article 54(3) EPC over its own divisional application.

1.11 The appellant submitted, that the legal issues arising from this objection were not complicated and that admitting the novelty objection at this stage of the proceedings would not lead to a significant delay of the procedures.

1.12 The board is of the opinion that a sound assessment of the question whether a divisional patent application could anticipate subject matter of its own parental patent application requires a substantial amount of legal analysis which would unavoidably lead to an adjournment of the proceedings. In view of the late filing, i.e. less than two months before oral proceedings were held, in accordance with Article 13(3)

RPBA, the board decides not to admit the late filed objection under Article 54(3) EPC into the proceedings.

Late filed documents

1.13 Document D65 and the corresponding priority document D70 were filed in response to the proprietor's response to the grounds of appeal. As a consequence thereto, the respondent filed amended claim requests. Under these circumstances, the board decides to admit documents D65 and D70 into the proceedings.

1.14 Document D86 filed by the respondent is identical with document D100 filed by the appellant. Since both parties and the board considered this document relevant, it was admitted.

1.15 Documents D90 and D101 to D103 were filed by the respondent and the appellant, respectively, in response to the board's communication. Both parties agreed to their introduction and the board decided to admit them.

Admissibility of the Main request

1.16 In point 4 of its communication attached to the summons to oral proceedings, the board had indicated that a decision on the admissibility of documents D65 and D70 would be taken at the oral proceedings. It had also indicated that it would most likely admit further submissions filed in direct response to the admission of the late filed documents.

The main request filed at the oral proceedings contains amendments which are a direct response to the admission

of documents D65 and D70 into the proceedings. Under these circumstances the board decides to admit the main request.

Articles 123(2), 123(3) and 84 EPC

2. In view of the board's decision on the admissibility of Article 100(c) EPC as a ground of opposition (cf. points 1.1. to 1.5 above) and the fact that amended claim 20 is the result of the incorporation of the features of dependent claims 22 and 28 as granted into independent claim 20 as granted, in accordance with the cross references stated therein, the amendments in claim 20 are not open to an objection under Article 123(2) EPC (cf. e.g. decision T 367/96 of 3 December 1997).

3. The appellant did not raise any objections under Articles 123(2), 123(3), and 84 EPC, and the board sees no need to do this on its own motion.

Article 83 EPC

4. The parties have not disputed, and the post published documents (e.g. D33, D38, D42, D48, D86) confirm, that the protein Sclerostin, identified in the patent under appeal by a positional cloning approach, plays a role in inhibiting bone growth and therefore represents a plausible target for controlling bone growth. There was also agreement that the skilled person could readily produce antibodies against Sclerostin. An objection under Article 83 EPC was only raised against claim 25.

5. Claim 25 refers to the use of an antibody according to claim 20 for the manufacture of a medicament for increasing bone mineralization.

6. The appellant submitted that the patent erroneously taught a direct interaction between Sclerostin and BMPs, and erroneously taught that the disruption of this interaction by antibodies affected bone mineralisation. The skilled person following this teaching could not obtain any medically useful antibodies, because the interactions described in Example 5 were artefacts. Moreover, the patent did neither disclose a single antibody affecting bone mineralisation nor identify regions of Sclerostin important to its physiological function. Therefore, as far as claim 25 was concerned, the skilled person was not in a position to readily identify antibodies suitable for medical use.

7. The language of claim 25 does not require the inhibition of a particular interaction. Thus, although there was a controversial discussion about the exact mode of action of Sclerostin, the answer to the question of sufficiency of disclosure does not depend on its outcome, as long as the skilled person could readily perform tests to establish whether an antibody had an effect on bone mineralisation.

8. The board will therefore first establish whether such assays were readily available.

9. In relation to medical uses, the patent teaches methods for determining whether a selected molecule is capable of increasing bone mineral content, comprising the "steps of (a) mixing a selected molecule with TGF-beta

binding protein and a selected member of the TGF-beta family of proteins, (b) determining whether the selected molecule stimulates signalling by the TGF-beta family of proteins, or inhibits the binding of the TGF-beta binding protein to the TGF-beta family of proteins" (cf. paragraphs [0030, 0139]. While methods for assaying a direct interaction between Sclerostin and BMPs are disclosed in more detail in Example 5, the patent does not further specify how the skilled person would analyse signalling by TGF-beta family proteins.

10. The appellant, in the context of its attack on inventive step, submitted that tissue culture tests would have been obvious to perform in various established systems in order to assess the role of candidate molecules in bone formation (cf. document D51, point 7, and Annex EW6). Known test systems included osteoblast cell lines such as MC3T3-E1 or ROS 17/2.8, primary osteoblast-enriched cell cultures (e.g. rat calvaria cells), or cartilage-derived primary chondroblasts/chondrocytes from chicken or rat. Alternatively, organ cultures from chicken sterna or rat calvaria could be established. Common markers of bone mineralization included osteocalcin or alkaline phosphatase. Animal studies could then be used to validate any observed effects.

11. Such assay systems have also been used to establish the role of BMPs in bone morphogenesis, i.e. to assay BMP mediated signalling (cf. e.g. Ruppert et al., 1996, attached to D59), and the board has no doubts that the skilled person could have used them not only for assaying the role of a candidate protein in the inhibition of bone mineralization, but also for

assaying the effects of potential inhibitors of the inhibitor of bone formation. The appellant arrived at the same conclusion in point 5 of annex EW6, attached to declaration D51.

12. Evidence that alkaline phosphatase and mineralization assays based on Mouse MC3T3 cells, BMP2, Sclerostin and anti-Sclerostin antibodies yield useful results is disclosed in post published document D58. This document discloses affinity selected anti-Sclerostin antibody fragments which were assayed for an effect on the inhibition of alkaline phosphatase activity by Sclerostin (Example 4). While most of the antibody fragments were ineffective, some showed variable degrees of reversal of the effect of Sclerostin. The best antibody inhibited the activity of Sclerostin by about 75 to 85%, albeit at an antibody concentration deemed too high. As further shown in Example 7, mineralization assays based on Mouse MC3T3 cells, Sclerostin and BMP-2 yield measurable effects of anti-Sclerostin antibodies on calcium deposition (Figure 2).

13. As mentioned above, the parties discussed the mode of action of Sclerostin and the ensuing consequences for the identification of neutralizing antibodies extensively and controversially. Apart from the patent itself, some post published documents such as e.g. document D33 disclosed an effect of Sclerostin on BMP signalling (cf. Fig. 4) while others disclosed an important mode of action of Sclerostin via Wnt signalling (documents D40 to D42).

14. To clarify this point, both parties submitted document D86, disclosing an important extracellular interaction

between Sclerostin and the Wnt protein, and an intracellular interaction between Sclerostin and BMP7.

15. In the board's view, detailed knowledge of the actual mode of action of Sclerostin might be useful for further optimizing screening procedures for the finding of therapeutically useful antibodies (cf. Example 2 of D48, and by Example 6 of D58). However, as long as the skilled person could identify at least some therapeutically useful antibodies on the basis of known in vitro assays (cf. points 12 and 13 above), even though this might have involved a serious effort, this additional detailed knowledge was not essential for performing the claimed invention without undue burden.

16. The appellant has further argued that even if the skilled person would have identified antibodies affecting the expression of e.g. alkaline phosphatase in osteoblasts, such antibodies were far from being clinically useful.

17. The patent system takes account of the intrinsic difficulties and the boards of appeal have accepted that for a sufficient disclosure of a therapeutic application, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported. Yet, this does not mean that a simple verbal statement in a patent specification that compound X may be used to treat disease Y is enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical. It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on

a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se. Showing a pharmaceutical effect in vitro may be sufficient if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application (T 241/95, OJ EPO 2001, 103, point 4.1.2 of the reasons, see also T 158/96 of 28 October 1998, point 3.5.2 of the reasons) or, as decision T 158/96 also put it, if there is a "clear and accepted established relationship" between the shown physiological activities and the disease (cf. point 9 of decision T 609/02).

18. In the present case, the patent clearly and undisputedly discloses a new protein, Sclerostin, and establishes it as a target for medical intervention in diseases of low bone density. Sclerostin is disclosed as an inhibitor of bone growth, and the patent teaches a way of identifying neutralizing antibodies of potential medical use by reference to functional assays. Asking for further proof of medical usefulness goes beyond the standards for assessing sufficiency of disclosure as set out by e.g. decision T 609/02 of 27 April 2004. Therefore the appellant's argument must fail.

19. In summary, the facts on file do not support the appellant's argument that the identification of neutralizing antibodies represented an undue burden.

As the skilled person was in a position to identify a neutralizing antibody readily and without undue burden,

the board decides that the invention according to claim 25 is sufficiently disclosed (Article 83 EPC).

Article 54(3) EPC

20. The appellant raised a novelty objection against claim 20 in view of document D65.

21. Claim 20 refers to monoclonal antibodies binding to the proteins encoded by any of the recited SEQ IDs (cf. item XIV above) with a Ka of greater than or equal to 10^8 M^{-1} but do not bind the protein Dan or the protein Gremlin. Subject matter defined in this way is not disclosed in the priority document of the patent under appeal, and thus, the relevant date for establishing novelty is the date of filing.

22. Document D65 constitutes prior art under Article 54(3) EPC, claiming priority from i.a. US provisional application 60/151700 (document D70). The filing date of this priority application is 31 August 1999 i.e. after the priority date but before the filing date of the patent under appeal.

23. Document D65 and its priority document D70 disclose a gene encoding a protein termed PRO7476. The encoded protein is completely identical with Sclerostin as defined by SEQ ID 2 in the patent under appeal. The nucleic acid sequence encoding PRO7476 differs from all the nucleic acid sequences recited in claim 1 of the patent under appeal. The protein of Seq ID 2 was disclosed in the priority application, and all other protein sequences recited in claim 19 differ from that

of PRO7476. Hence claims 1 and 19 are not affected by the disclosure of document D65.

24. Document D65 and its priority document furthermore disclose antibodies specifically binding to PRO7476 (D65, claim 2; D70, claim 34) and provide a general teaching how to raise poly- and monoclonal antibodies (D65, pages 71 to 76; D70, pages 49 to 58).

25. Referring to [0116] of the patent under appeal, where antibodies specifically binding were defined as antibodies specifically binding with the protein of SEQ ID 2 but not with i.a. Dan or Gremlin, the appellant argued that monoclonal antibodies specifically binding with PRO7476 fell within the scope of claim 20. The limitation of the claim to monoclonal antibodies with a Ka of greater than or equal to 10^8 M^{-1} could not help in overcoming this objection because, as shown by documents D101 to D103, the average Ka of monoclonal antibodies was 10^8 M^{-1} and the majority of the monoclonal antibodies raised would be expected to have a Ka greater than this value.

26. According to the evidence on file, common Ka values of antibodies range from $5x10^4$ to 10^{11} M^{-1} (D90), 10^5 to 10^{12} M^{-1} (D101), 10^7 to 10^{10} M^{-1} (D102), and 10^8 to 10^{12} M^{-1} (D103). Thus, a reference to an antibody specifically binding with a particular protein encompasses antibodies with affinity constants ranging from clearly below 10^8 M^{-1} up to 10^{12} M^{-1}.

Claim 20 is limited to antibodies binding to Sclerostin with a Ka of greater than or equal to 10^8 M^{-1}, hence to a subgroup of all those antibodies that the skilled

person following the teaching of document D65 would obtain. Such a subgroup is however neither explicitly nor implicitly disclosed in document D65.

27. Thus, the board decides that the subject matter of claim 20 is novel.

Article 56 EPC

28. Document D3 represents the closest prior art. It discloses a genetic locus on human chromosome 17 linked to Van Buchem disease, a disease characterized by increased bone formation. The authors identified a candidate region of <1 cM between two specific markers, and noted that a number of genes had already been assigned to this chromosomal region. They concluded that detailed physical mapping of the known genes in relation to the candidate locus should help in reducing the number of candidate genes. It was also noted that the clinical symptoms of Van Buchem disease resembled those of sclerosteosis. Based on the mode of inheritance in Van Buchem patients, the authors speculated that the disease causing mutation led to a loss of function of the unknown gene, and that antisense treatment might become a form of therapy for diseases linked to low bone density.

29. In light of this disclosure, the technical problem underlying the present invention can be seen in the provision of a target for therapy of diseases linked to low bone density.

30. For the solution of this problem, the patent proposes the isolated nucleic acid molecules of claim 1 and the proteins of claim 19.

31. As shown in example 1, the gene identified as encoding Sclerostin comprises a non-sense mutation unique to sclerosteosis patients which plausibly explains the observed phenotype. The board is therefore satisfied that the above mentioned problem has indeed been solved.

32. It remains to be established if the claimed solution involves an inventive step.

33. The appellant submitted that the skilled person, starting from document D3, would have arrived at the claimed solution on the basis of in silico analyses and without inventive skills. Prompted by document D3, the skilled person would have probed databases for clones in the candidate region of D3, would have entered the clones in a gene prediction program, would have found a limited number of genes, most of which were not of interest, and would finally have arrived at a candidate gene with some homology with a bone related protein. This candidate gene, which encodes Sclerostin, was the obvious solution to the technical problem mentioned above.

34. The board has no doubts that the skilled person, at the date of filing had the necessary skills to perform in silico analyses on the basis of the available genomic and other databases. The board does however not agree that the skilled person would have arrived at the claimed solution in an obvious way.

35. As it turned out later, the 0.7 cM region mentioned in document D3 encompasses about 3.4 megabases (page 10 of respondent's letter of 15 April 2010) most of which (about 85%) had not been sequenced at the filing date. It is not apparent why the skilled person would have a priori limited its analysis to only those regions between the genetic markers which had already been sequenced and would have further reduced the number of candidate genes on the basis of often hypothetical functional annotations (note in this context that PRO7476 of document D65 was identified in a search for growth factor homologs; cf. also the contradicting expert declarations D51, D68, and D61).

36. Moreover, even if the skilled person would have limited its strategy to analysing the publicly available data bases as suggested by the appellant, and would have arrived at a most promising gene sequence displaying some homology with the protein Dan, the obvious next step for further analysis of this candidate gene would have been to look for mutations in the gene in Van Buchem patients in order to explain the observed phenotype. The skilled person could however not have confirmed a role of the candidate gene in Van Buchem disease because the gene is not mutated in those patients. (cf. document D22, showing that the mutation underlying Van Buchem disease is located in a regulatory region considerably upstream of the gene, which had not yet been sequenced at the date of filing).

37. The appellant further submitted that the skilled person could have looked for mutations in the candidate gene in sclerosteosis patients.

38. This approach is based on hindsight because, although a locus had been mapped in Van Buchem patients, document D3 (page 398, left column, 2nd paragraph) merely suggested that the localization of the Van Buchem disease gene would allow the testing of the hypothesis that dominant endosteal hyperosteosis and/or sclerosteosis were allelic to Van Buchem disease. In other words, the idea that the genetic alteration underlying both diseases affected the same gene was speculative.

39. The appellant further submitted that the skilled person could have tested the candidate gene for an effect on bone formation on the basis of readily available in vitro assays. There is however no evidence that only one of the candidate genes in this region of the genome would have shown an effect in one or more of the known assays for bone formation.

40. In summary, the skilled person, following the in silico approach suggested by the appellant, would have had to take multiple decisions along the way to arrive at the claimed solution. This included decisions concerning the inclusion or exclusion of non-annotated sequences, a pre-selection of likely candidates genes on the basis of functional annotations, a narrowing down of the preselected genes on the basis of sequence homologies, a selection from multiple options for verifying the link to the observed phenotype (analysis of the gene in patients with Van Buchem disease, in patients with sclerosteosis or (one or several) in vitro assays for bone formation). At each point, the skilled person would have to take the right decision to arrive at the

claimed solution in an obvious way. This is only possible with hindsight.

41. According to the established case law, the question to be asked in respect of inventive step is not whether the skilled could have arrived at the claimed solution but whether it would have arrived at the solution with a reasonable expectation of success.

42. The board concludes that the skilled person, starting from document D3 and using its general knowledge would not have arrived at the claimed solution in an obvious way.

Therefore, the board decides that the subject matter of claims 1 to 41 of the main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of claims 1 to 41 of the Main Request filed at the oral proceedings before the board and a description to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski M. Wieser