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Datasheet for the decision of 20 February 2014

Case Number: T 2329/10 - 3.3.08

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Language of the proceedings: EN

Title of invention:
OSTEOPROTEGERIN BINDING PROTEINS AND RECEPTORS

Patent Proprietor:
Amgen Inc.,

Opponents:
Schering Corporation
Ablynx N.V.

Headword:
Osteoclastogenesis bone disease osteoporosis/AMGEN

Relevant legal provisions:
EPC Art. 123(2), 123(3), 83, 54, 56
RPBA Art. 12(4), 13(1)

Keyword:
Admissibility of Main Request (yes)
Amendments - extension beyond the content of the application as filed (no)
Sufficiency of disclosure - (yes)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:
T 0019/90, T 0207/94, T 0715/03

Catchword:

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Case Number: T 2329/10 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 20 February 2014

Appellant: (Patent Proprietor)	Amgen Inc., One Amgen Center Drive Thousand Oaks, California 91320-1799 (US)
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Respondent: (Opponent 2)	Ablynx N.V. Technologiepark 21 9052 Ghent-Zwijnaarde (BE)
Representative:	Boult Wade Tennant Verulam Gardens 70 Gray's Inn Road London WC1X 8BT (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 15 October 2010 revoking European patent No. 975754 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman:	M. Wieser
Members:	P. Julià
	C. Heath

Summary of Facts and Submissions

I. European patent No. 0 975 754, a divisional application of the earlier European patent application No. 06 015 956, was published as International patent application WO 98/46751 (hereinafter "*the application as filed*"), and granted with 13 claims. Claim 1 read as follows:

"1. Use of an antibody as a modulator of osteoprotegerin binding protein (OPGbp) for the preparation of a medicament for preventing or treating bone disease, wherein the antibody or fragment thereof is an antagonist which binds to OPGbp of Figures 4 A-F (SEQ ID NO: 4)."

Claims 2 to 13 were directed to preferred embodiments of claim 1.

II. Two oppositions were filed against the patent on the grounds of Articles 100(a),(b) and (c) EPC. In its decision of 15 October 2010, the opposition division considered the Main Request and Auxiliary Requests I and II to contravene Article 123(2) EPC, and Auxiliary Requests III to VIII not to involve an inventive step (Article 56 EPC). Accordingly, the patent was revoked.

III. The patentee (appellant) lodged an appeal and, with the statement of Grounds of Appeal, filed a new Main Request and Auxiliary Requests I to XV.

IV. Both opponents 01 and 02 replied to the appellant's Grounds of Appeal. With letter dated 23 August 2011, opponent 01 withdrew its opposition.

V. On 23 September 2013, the board sent a communication pursuant to Article 15(1) of the Rules of Procedure of

the Boards of Appeal (RPBA) to the parties informing them of its preliminary opinion on the substantive issues of the appeal.

VI. With a letter dated 26 November 2013, the appellant replied to the communication and filed new Auxiliary Requests IB to XVB, and a new Auxiliary Request VIII to replace its former Auxiliary Request VIII.

VII. With a letter filed on 20 January 2014, the appellant filed further submissions on the patentability of its requests.

VIII. With a letter dated 20 December 2013, opponent 02 (respondent) informed the board of its intention not to attend the oral proceedings and the maintenance of all its requests.

IX. Oral proceedings took place on 20 February 2014 in the presence of the appellant. In the course of these proceedings, the appellant made its former Auxiliary Request VIB its Main Request and withdrew all other claim requests.

X. Claim 1 of the Main Request read as follows:

"1. Use of an antibody as a modulator of osteoprotegerin binding protein (OPGbp) for the preparation of a medicament for preventing or treating bone disease, wherein the antibody is an antagonist which binds to OPGbp of Figures 4 A-F (SEQ ID NO: 4) and inhibits OPGbp mediated osteoclastogenesis and/or bone resorption."

Claims 2 to 10 were directed to preferred embodiments of claim 1 and read as claims 2-6, 8, 9, 11 and 12 as

granted, except for deletion of the term "*or fragment thereof*".

XI. The following documents are cited in the present decision:

CD1a: JP 097808/1997 (application date: 15 April 1997);

CD1y: EP-A1-0 911 342 (filing date: 15 April 1998);

CD2: W.S. Simonet et al., Cell, Vol. 89, 18 April 1997, pages 309 to 319;

CD4: H. Yasuda et al., Proc. Natl. Acad. Sci. USA, Vol. 95, March 1998, pages 3597 to 3602;

CD16: T. Suda et al., Bone, Vol. 17, No. 2 Supplement, August 1995, pages 87S to 91S;

CD17: E. Tsuda et al., Biochem. Biophys. Res. Commun., Vol. 234, May 1997, pages 137 to 142;

CD24-01: Sequences of the Extracellular Domain of RNAKL (rat, mouse and human), Annex C of document CD24.

XII. For the sake of simplicity, the board, in the present decision, refers only to osteoprotegerin (OPG) and to osteoprotegerin binding protein (OPGbp), even though documents on file refer to these products by using other designations, such as osteoclastogenesis inhibitory factor (OCIF) (documents CD1 and CD17), OPG/OCIF (document CD4) for OPG, and OCIF binding molecule (OBM) (document CD1), osteoclast differentiation factor (ODF) (document CD4) for OPGbp.

XIII. Appellant's submissions, insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of the new Main Request

The Main Request was originally filed as Auxiliary Request VIB in reply to the board's communication (Article 15(1) RPBA). This request was based on former Auxiliary Request VI, originally filed with the statement of Grounds of Appeal, which was identical to Auxiliary Request II in opposition proceedings, except for the deletion of the term "*or fragment thereof*" in order to overcome an objection under Article 123(2) EPC. Auxiliary Request VIB was distinguished from former Auxiliary Request VI by the deletion of claim 11 only, which had been objected by the board.

Article 100(c) EPC - Article 123(2) EPC

Claims 34 and 36 of the application as filed were directed to methods of preventing or treating bone diseases by administration of an OPGbp modulator, wherein the modulator was an antibody. In the application as filed, human OPGbp of Figure 4 A-F (SEQ ID NO:4) was a preferred OPGbp embodiment. In the section on pages 18-19 devoted to explaining the antibodies of the invention, the preferred antibodies were antagonist antibodies. On page 19, therapeutic uses for antibodies binding to OPGbp and blocking the interaction with other binding compounds (antagonist antibodies) were contemplated.

Article 100(b) EPC - Article 83 EPC; Article 100(a) EPC - Article 54 EPC

The findings of the opposition division as regards Articles 83 and 54 EPC applied to the Main Request. As regards Article 83 EPC, the patent characterized OPGbp and showed its involvement in mediating the OPG effects on osteoclastogenesis (Examples 1-7 of the patent). Recombinant soluble OPGbp was shown to stimulate the formation of functional osteoclasts and to replace both stromal cells and steroids in an *in vitro* osteoclast assay (Example 8). *In vivo* osteoclast activity and increased bone resorption was induced by recombinant soluble OPGbp in a mouse model (Example 9). Both activities could be inhibited by addition of OPG. Loop structures of OPGbp were identified as potential targets for antibodies that could block the interaction of OPGbp with its receptor (Example 11). Thus, it was credible that an antibody binding to OPGbp and acting as an antagonist could have an effect in bone disease and be therapeutic effective in bone disease.

Article 100(a) EPC - Article 56 EPC

Document CD2, the closest prior art, disclosed murine OPG and showed that it negatively regulated osteoclast maturation and increased bone density *in vivo*. The use of OPG for the treatment of bone diseases was also disclosed in document CD2. Starting from document CD2, the technical problem to be solved was the provision of a novel therapy for bone diseases such as osteoporosis. Based on the patent, in particular Examples 8 and 9, the claimed subject-matter credibly solved the problem.

Since document CD2 disclosed OPG, the obvious route for a skilled person to follow was the further development of OPG as a therapeutic agent for bone diseases. There was no motivation to look for the OPG binding partners suggested in document CD2. The less so in view of the

unique nature of OPG (first soluble (putative) member of the TNF family), the unknown nature and number of possible OPG binding partners (one or several ligands and/or receptors) and their role in osteoclastogenesis. Document CD17, which also disclosed murine OPG and its binding to murine ST2 stromal cells, suggested possible alternative OPG binding partners and indicated that their investigation was urgent, only and exclusively, for clarifying the mechanism by which OPG inhibited osteoclastogenesis. However, document CD17 was silent on any therapeutic use. When applying the "could/would test" defined in the case law, the skilled person would not have engaged in such a high risk approach but would rather have pursued the much more promising route provided by the disclosure of OPG itself.

Even if only for scientific purposes, a skilled person would have followed the suggestion of document CD17 to clone cDNA encoding the OPG binding partner(s), real technical difficulties would have been encountered. Document CD17 showed OPG to be a heparin-binding basic glycoprotein exhibiting a high level of non-specific binding to other proteins. The use of OPG as a probe for expression cloning of binding partner(s) required a specific technique with labeled OPG in presence of high amounts of unlabeled OPG as shown in post-published document CD4. Moreover, evidence was on file showing an OPG binding receptor (TRAIL) other than the OPGbp disclosed in the patent. An affinity purification of OPGbp from murine ST2 cells was not free of difficulties, since ST2 cells were adherent cells and required to be released before their use for screening. However, standard proteolytic methods would have degraded any hypothetical membrane protein to which OPG could potentially bind.

In view of the unique nature of OPG, the unknown OPG binding partners and their role in osteoclastogenesis, a skilled person, starting from document CD2 or from any other document on file (documents CD16 or CD17), would not have had, without knowledge of Examples 8 and 9 of the patent, any reasonable expectation of success to arrive at a therapeutic use for an antagonist anti-OPGbp antibody (cf. *inter alia*, T 715/03 of 16 January 2006).

XIV. The respondent did not specifically raise any objections against the Main Request (originally filed as Auxiliary Request VIB). However, the submissions put forward against the claim requests filed with the appellant's Grounds of Appeal are also relevant for this request and may be summarized as follows:

Admissibility

In reply to the appellant's Grounds of Appeal, no objections were raised against the admissibility of the new claim requests, and no reply was filed to the board's communication in which the admissibility of these new requests was considered.

Article 100(c) EPC - Article 123(2) EPC

The medical use of antagonist anti-OPGbp antibodies in the treatment of bone diseases in general was not disclosed in the application as filed. The passage on page 19 failed to define an antagonist antibody and merely stated that antibodies binding to OPGbp and blocking the interaction with other binding compounds could have a therapeutic use in the modulation of osteoclast differentiation. However, it was known that

OPGbp interacted with at least two different binding compounds: OPG and ODAR/RANK, and it was not clear from this passage on page 19 which interaction should be blocked. Moreover, the term "*modulation*" embraced both an increase and a decrease in the activities associated with OPGbp.

There was no disclosure in the application as filed of an antibody binding to the human OPGbp of Figure 4 A-F (SEQ ID NO:4), let alone of a medical use for these antibodies. Original claims 25, 34 and 36 referred to antibodies binding to OPGbp in general. Likewise, the section on page 19 of the application as filed describing antibodies for potential therapeutical use referred only to antibodies to OPGbp in general. Antibodies binding to human OPGbp were a selection from all possible antibodies binding to OPGbp in general. This selection was not disclosed in the application as filed and the medical use of human antibodies was not directly derivable from it. According to the case law, an implicit disclosure should not be construed to mean matter that did not belong to the content of the technical information provided by a document but was merely rendered obvious on the basis of that content.

Article 100(b) EPC - Article 83 EPC

The biological function of OPGbp in osteoclast differentiation was already predicted in the prior art (documents CD16, CD17). The patent did not go beyond this disclosure, since it did not demonstrate a therapeutic benefit arising from administration of an anti-OPGbp antibody. There was no experimental evidence whatsoever that an antibody capable of binding to OPGbp with sequence SEQ ID NO:4 would produce a useful

physiological effect of therapeutic potential when administered to a human subject. According to the case law, in the absence of such evidence, the requirements of Article 83 EPC were not fulfilled. If the effect of an antagonist anti-OPGbp antibody was predictable based solely on the knowledge of the biological function of OPGbp in promoting osteoclast differentiation, then this had implications for Article 56 EPC, since this function was already known in the prior art (documents CD16, CD17).

Article 100(a) - Article 54 EPC

The set of antibodies disclosed in documents CD1/CD1a overlapped with the set of antibodies binding to the OPGbp of sequence SEQ ID NO:4. Document CD1/CD1a disclosed the use of such antibodies in therapy of bone metabolism, such as osteoporosis, and it further taught that antibodies neutralizing the biological activity of OPGbp, i.e. induction of osteoclast formation (osteoclastogenesis), were useful for the treatment or prevention of bone metabolism abnormality. The activity of anti-OPGbp antibodies to neutralise the OPGbp biological activity was measured in document CD1/CD1a by the suppression of osteoclast formation in an *in vitro* assay system known from the prior art.

Article 100(a) EPC - Article 56 EPC

According to a first line of argument, the respondent adopted the problem-solution approach followed in the decision under appeal. Document CD2, the closest prior art document, disclosed OPG as a secreted glycoprotein regulating bone resorption and showed that the administration of recombinant OPG inhibited osteoclastogenesis. Starting from this prior art, the

technical problem to be solved was the provision of alternative compounds for the treatment of osteopenic diseases associated with increased osteoclast activity. The use of the antagonist anti-OPGbp antibodies of claim 1 provided a solution to this problem. Document CD2 already discussed the existence of an OPG binding partner, namely a TNF-related protein acting as an osteoclast maturation factor. Thereby, document CD2 provided both a motivation to identify this OPGbp and a reasonable expectation of success, since it disclosed a binding partner (OPG) to use as a bait, a function to test and a suitable source (ST2 cells). OPG was also disclosed in document CD17 which also referred to an OPG binding partner. No difficulties were to be expected in the cloning of OPGbp and none were encountered as shown by the post-published document CD4. The cloning of mouse OPGbp was the starting point for cloning the homologue human OPGbp and the provision of antagonist anti-oPGbp antibodies followed therefrom as a routine measure.

A second line of argument was based on document CD16, alone or in combination with either documents CD17 or CD2. Document CD16 identified a membrane-bound factor on ST2 cells as a key factor in osteoclast differentiation. This document indicated that the model of osteoclast differentiation, as described in Figure 3, could be used to produce new ways for treating several metabolic bone diseases caused by abnormal osteoclast recruitment. Thus, the technical problem to be solved was the provision of new therapeutic agents for the treatment of bone diseases. The use of antagonist antibodies against human OPGbp of sequence SEQ ID NO:4 was a solution also to this problem. However, there was no indication in the patent, let alone any experimental evidence, that such antagonist

antibodies had any therapeutic efficiency in the treatment of the wide range of bone diseases encompassed within the scope of the claims. Both, documents CD17 and CD2, provided OPG and ST2 cells as the starting material for expression cDNA cloning or affinity purification of OPGbp. The isolation of OPGbp was a matter of routine experimentation as shown by post-published document CD4. The preparation of antibodies was common general knowledge requiring only routine techniques. Indeed, it was not even essential to have OPGbp in purified form since antibodies could be raised by other means, such as using ST2 membrane fractions. Likewise, the selection and use of antagonist anti-OPGbp antibodies did not require any inventive effort.

XV. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained based on the Main Request filed during the oral proceedings before the board.

XVI. The respondent (opponent 02) requested in writing that the appeal be dismissed.

Reasons for the Decision

Admissibility of the Main Request

1. The Main Request was originally filed as Auxiliary Request VIB in reply to the board's communication pursuant to Article 15(1) RPBA (cf. points V and VI *supra*). Auxiliary Request VIB was identical to Auxiliary Request VI except for the deletion of claim 11. The deletion was made in order to overcome objections raised by the board under Articles 123(3)

and 84 EPC against the amendments introduced into claim 11 (granted claim 13). Auxiliary Request VI had been filed with the appellant's Grounds of Appeal (cf. point III *supra*) and, apart from the deletion of the term "*or fragment thereof*" (to overcome an objection under Article 123(2) EPC), was identical to Auxiliary Request II in the opposition division proceedings.

2. The amendments introduced into the Main Request were thus made in reply to objections raised by the board, did not add complexity to the case and were in line with the principle of procedural efficiency. Thus, the board, exercising its discretion, admits the Main Request into the appeal proceedings (Articles 12 and 13(1) RPBA).

Article 84 EPC

3. None of the amendments introduced into the Main Request is ambiguous *per se* and/or introduces clarity issues. Except for the deletion of several dependent claims (granted claims 7, 10 and 13), of the term "*or fragment thereof*" and for the introduction into claim 1 of the feature "*inhibits OPGbp mediated osteoclastogenesis and/or bone resorption*", the Main Request is identical to the granted claims (cf. points I and X *supra*). Thus, the requirements of Article 84 EPC are met.

Article 100(c) EPC - Articles 123(2) and (3) EPC

4. The amendments introduced into the Main Request overcome several objections under Article 123(2) EPC in view of the requests considered by the opposition division (cf. pages 4-14 of the decision under appeal).

5. Page 19, lines 15-26 of the application as filed dicloses a therapeutic use of anti-OPGbp antibodies that bind to OPGbp and inhibit OPGbp mediated osteoclastogenesis and/or bone resorption in the treatment of bone disease. These two features define these (modulating) antibodies as being antagonists (cf. page 19, lines 26-31 of the application as filed). This disclosure is in line with claims 34 and 36 as originally filed, with the definition of "modulator" given on page 23, line 28 to page 24, line 7, and with page 24, lines 25-28 and page 30, lines 9-14 of the application as filed.

6. Moreover, in the light of the application taken as a whole and the disclosure of the specific human OPGbp of Figures 4 A-F (SEQ ID NO: 4) as a preferred embodiment (cf. *inter alia* page 12, lines 12-14 and page 15, lines 25-27 of the application as filed), the passages on page 19 have to be understood to apply, implicitly, to antagonist antibodies of the preferred embodiment, i.e. human OPGbp of Figures 4 A-F (SEQ ID NO: 4).

7. Thus, the Main Request fulfils the requirements of Article 123(2) EPC. The requirements of Article 123(3) EPC are also fulfilled, since the amendments introduced into the Main Request do not extend the protection conferred by the granted patent.

Article 100(b) EPC - Article 83 EPC

8. The respondent contested the findings of the opposition division on Article 83 EPC and referred to its submissions during the opposition procedure, wherein it particularly noted that the patent did not contain any experimental evidence for the claimed subject-matter (cf. point XIV *supra*).

9. According to the case law of the Boards of Appeal, when a therapeutic application is claimed, attaining the claimed therapeutic effect is a functional feature of the claim. In this case, the requirements of Article 83 EPC are fulfilled if the patent discloses the suitability of a substance for the claimed application. There is no need to provide clinical trials or experimental evidence in animals to prove its suitability, a therapeutic effect may well be acknowledged on the basis of any data that shows a clear relationship between the physiological activities of this substance and the disease, or a direct effect of this substance on a metabolic mechanism specifically involved in the disease (cf. "Case Law of the Boards of Appeal of the EPO", 7th edition 2013, II.C.6.2, page 318).

10. In fact, based on the experimental data disclosed in the patent, the opposition division considered that it is "*credible that antagonistic antibodies against OPGbp should have an effect in bone disease ... and it is furthermore plausible to expect that a therapeutical effect will be present even for diseases of decreased bone formation*" (cf. page 16, last paragraph to page 17, first two paragraphs of the decision under appeal). In reply to appellant's Grounds of Appeal, the respondent did not provide any further evidence to convince the board that the decision of the opposition division in this regard has to be overturned.

11. The results shown in Examples 8 and 9 of the patent are highly relevant. The fact that OPGbp *in vitro* acts as an osteoclastogenesis stimulating (differentiation) factor and *in vivo* promotes bone resorption, leading to systemic hypercalcemia (cf. page 17, Examples 8 and 9

of the patent), renders the claimed therapeutic effect credible. In view thereof and since no serious doubts, certainly not substantiated by verifiable facts (cf. *inter alia*, T 19/90, OJ EPO 1990, page 476), arise as to the correctness of the findings of the opposition division, the board sees no reason to deviate from the decision of the opposition division as regards Article 83 EPC. Thus, the Main Request fulfils the requirements of Article 83 EPC.

Article 100(a) EPC - Article 54 EPC

12. The findings of the opposition division with regard to the priority rights of the patent have not been contested by the appellant. The human OPGbp of Figures 4 A-F (SEQ ID NO:4) is not disclosed in the first priority document (US 842842, 16 April 1997). Thus, the effective date for the subject-matter of the Main Request is 23 June 1997 (US 880855) (cf. page 15, second paragraph of the decision under appeal and page 15, point 4 of the appellant's Grounds of Appeal).

13. Document CD1a, the first priority document of document CD1y, is the sole document cited in appeal proceedings under Article 54(3) EPC. Although there is a reference to osteoblastic human cells as starting material for isolation of OPGbp (cf. page 10, lines 15 to 19), document CD1a discloses only the isolation and purification of murine OPGbp (cf. Examples 1 and 2, page 22 to page 27). There is no disclosure of human OPGbp with the sequence of Figures 4 A-F (SEQ ID NO:4). Document CD1a also discloses the biological activity of murine OPGbp to support or promote osteoclast differentiation and maturation (cf. *inter alia*, page 7, line 22 to page 8, line 2, pages 33 to 36, Example 5), and its use for preventing or treating diseases related

to bone metabolism (cf. *inter alia*, page 8, lines 8 to 15). In this context, reference is made to pharmaceutical compositions comprising OPGbp or antibodies thereto (cf. *inter alia*, page 8, line 23 to page 9, line 2, claims 7 and 8).

14. It was argued that, in view of the high degree of homology between the amino acid sequences of murine and human OPGbp (cf. Annex C of document CD24-O1, which shows part of their extracellular domain, including the BB' and EF loops of residues 172-198 and 241-257, respectively; Example 11 of the patent), there might be antibodies raised against murine OPGbp that would bind to epitopes shared with human OPGbp, i.e. that would cross-react with human OPGbp. However, not all antibodies raised against murine OPGbp will be modulators. Whereas some antibodies may have no effect on OPGbp at all (on its activity, ligand and/or receptor binding, etc.), others may be agonists or antagonists resulting in an increased or decreased OPGbp activity and may or may not have a therapeutic application in the diseases mentioned in document CD1a (cf. *inter alia*, page 4, lines 14 to 17).

15. However, document CD1a refers to murine anti-OPGbp antibodies in general terms only. There is no distinction of agonist and antagonist antibodies, no characterization of epitopes which raise these two types of antibodies, let alone a disclosure of murine anti-OPGbp antibodies cross-reacting with human OPGbp. This subject-matter is not clearly and unambiguously derivable from document CD1a.

16. Therefore, there is no reason for the board to deviate from the decision of the opposition division as regards the disclosure in document CD1a. The Main Request is

considered to fulfil the requirements of Article 54 EPC.

Article 100(a) EPC - Article 56 EPC

17. Before applying the problem and solution approach (cf. "Case Law", *supra*, I.D.2, page 165), it is important to note that claim 1 of the Main Request is not a product claim directed to OPGbp in general, to the specific human OPGbp of Figures 4 A-F (SEQ ID NO:4) or to antibodies thereto. Claim 1 is directed to a medical use ("*use of ... for the preparation of a medicament for preventing or treating bone disease*") of a particular product ("*antibody*") defined by specific technical features ("*an antagonist which binds to OPGbp of Figures 4 A-F (SEQ ID NO:4) and inhibits OPGbp mediated osteoclastogenesis and/or bone resorption*") (cf. point X *supra*). For this type of claims, a substantial body of case law has been developed concerning the criteria for assessing sufficiency of disclosure (cf. point 9 *supra*), novelty and inventive step (cf. *inter alia*, T 715/03, *supra*).

Closest prior art

18. In line with the opposition division (cf. page 25 of the decision under appeal), document CD2 is considered to represent the closest prior art document.

Document CD2 discloses the isolation and purification of OPG, a secreted protein, member of the tumor necrosis factor receptor (TNFR) superfamily, involved in the regulation of bone mass or density (cf. page 309, left-column, Summary and right-hand column, third paragraph). Figure 1 discloses the alignment of the amino acid sequences of OPG from human, mouse and rat,

and shows that the mouse and human OPG proteins, respectively, are about 85% and 94% identical to the predicted rat protein (cf. page 310, Figure 1, page 309, right-hand column, last paragraph to page 311, left-hand column, first paragraph). *In vivo* osteoclast-forming assays and *in vitro* experiments (OPG administration to mice, generation of transgenic OPG mice) identify OPG as a soluble factor involved in the regulation of bone density (decrease of later stages of osteoclast differentiation, increase of bone density, blocking of ovariectomy-associated bone loss) (cf. page 312, left-hand column to page 316, left-hand column, page 317, right-hand column, last paragraph to page 318, right-hand column, first paragraph). These results are acknowledged to "*imply a utility for OPG in the treatment of osteoporosis associated with increased osteoclast activity*" (cf. page 309, left-hand column, last sentence of Summary and page 317, left-hand column last sentence of second paragraph).

There is no other prior art document on file disclosing, in such an explicit manner, the possible use of OPG for the treatment of bone diseases. This is true for the contemporaneous prior art document CD17 which discloses the isolation, purification and biological activity of OPG, or for document CD16, published earlier than documents CD2 and CD17 at a date when OPG had not yet been isolated and characterized.

Objective technical problem

19. Starting from the closest prior art, the objective technical problem to be solved is the provision of an alternative treatment for bone disease, such as osteoporosis. The solution proposed by the patent is

the use of an antagonist anti-OPGbp antibody that binds to OPGbp of Figures 4 A-F (SEQ ID NO:4) and inhibits OPGbp mediated osteoclastogenesis and/or bone resorption, i.e. the subject-matter of claim 1 and the preferred embodiments of claims 2 to 10 of the Main Request (cf. point X *supra*).

20. As stated in points 10 and 11 *supra*, the results shown in Example 8 and 9 of the patent render the claimed therapeutic effect, i.e. the solution proposed in the patent, credible.

Obviousness and reasonable expectation of success

21. Document CD2 reports of studies characterizing the OPG domain required for OPG activity (dose-dependent inhibition of osteoclast differentiation in an *in vitro* osteoclast-forming assay) (cf. page 315, left-hand column, first full paragraph). These studies lead the authors of document CD2 to the hypothesis that OPG may neutralize a TNF-related ligand or bind to a transmembrane TNF-related receptor (cf. page 316, right-hand column, last paragraph). However, it is explicitly acknowledged that the nature and number of these ligand(s) or receptor(s) is unknown (cf. page 316, right-hand column, last sentence of second paragraph).

22. Although there are no cross-references between documents CD2 and CD17, the board considers that, in view of the identical structural properties of the protein factors disclosed in both documents (cf. page 311, left-hand column, first paragraph in document CD2 and page 137, Abstract and paragraph bridging pages 138 and 139 of document CD17) as well as of their identical biological activity (inhibition of osteoclastogenesis),

a skilled person would readily have identified both factors as actually being the same entity, namely OPG. The more so, since the amino acid sequences of the three internal peptides of the protein factor disclosed in document CD17 can be easily identified within the amino acid sequence of human OPG shown in Figure 1 of document CD2 (residues 354-359 (P1), residues 243-255 (P2) and residues 368-378 (P3), Figure 1(B) of document CD2).

23. In view of the OPG activity, the authors of document CD17 speculate on the possible mechanism of OPG action on the inhibition of osteoclastogenesis. Among several alternatives, the authors of document CD17, based on the results of a "*preliminary binding study*" using [^{125}I]-OPG which shows that OPG "*specifically binds to ST2 stromal cells*", suggest the possible presence of "*a membrane-anchored protein involved in the signal transmission between ST2 cells and osteoclastic progenitor cells*" (cf. page 141, paragraph bridging left and right-hand columns). They further urge to pursue the investigation into the OPG binding molecule on osteoblastic cells for clarifying the mechanism by which OPG inhibits osteoclastogenesis. In this context, there is an explicit reference to "*cloning of complementary DNA (cDNA) encoding*" OPG (cf. page 141, right-hand column, last sentence of first paragraph).

24. In line with the opposition division (cf. paragraph bridging pages 25-26 of the decision under appeal), it may be argued that a skilled person, in view of these OPG binding studies using murine ST2 stromal cells, would have followed the suggestion made in document CD17 and would have tried to clone the OPG binding protein(s) using a murine ST2 expression cDNA library. However, in view of the fact that the nature, number

and (osteoblast, pre-osteoclast) cell location (which depends on the actual mechanism of OPG action) of the OPGbp binding protein(s) were far from clear (cf. page 13 of appellant's letter filed on 20 January 2014), it is arguable that such a situation can be equated to the "one-way-street" situation defined in the case law of the Boards of Appeal (cf. "Case Law", *supra*, I.D.10.8, page 229).

Moreover, as argued by the appellant, in view of the general unspecific binding properties of OPG, acknowledged in document CD17 to be "*a heparin-binding basic glycoprotein*" (cf. page 137, left-hand column, abstract and paragraph bridging pages 140-141 of document CD17), a skilled person would have encountered real difficulties when carrying out such a cloning approach (cf. *inter alia*, T 207/94, OJ EPO 1999, page 273). In particular, specific tools and conditions had to be selected in order to successfully use OPG as a bait for screening positive OPGbp clones (cf. page 3598, left-hand column, third paragraph of the post-published document CD4, cited as an expert opinion; point XIII *supra*).

25. However, the board does not consider it necessary to enter in detail into the merits of these arguments as it is convinced that a skilled person would not have put into practice the suggestion made in document CD17 when trying to solve the technical problem formulated above, i.e. achieving a successful treatment for bone disease (cf. "Case Law", *supra*, I.D.5, page 182). If he/she, nevertheless, would have done so, cloning of the murine OPGbp would only have been the first step for further identifying, isolating and characterizing a human OPGbp having a specific amino acid sequence (Figure 4 A-F, SEQ ID NO:4). This human OPGbp,

consequently, would have to be used then for the production of specific antagonist antibodies, i.e. the entity used for the medical use according to claim 1 of the Main Request.

26. Indeed, the board shares the appellant's view that in such situation an expectation of success could only be present with the knowledge of the results shown in Examples 8 and 9 of the patent. In particular, only the fact that OPGbp alone, i.e as such, is capable to replace "*the stroma and added steroids*" and to act "*as an osteoclastogenesis stimulating (differentiation) factor*" in the presence of M-CSF (cf. page 17, Example 8 of the patent), provide a reasonable expectation for a skilled person that antagonist anti-OPGbp antibodies according to claim 1 of the Main Request may indeed be suitable for use in the preparation of a medicament for preventing or treating bone disease. This expectation cannot be derived from the actual technical disclosure of documents CD2 or CD17, nor from the speculations and hypothesis discussed in these documents, and certainly not at the level required by the Boards of Appeal for claims referring to a medical use (cf. *inter alia*, T 715/03, *supra)*.

27. Thus, the Main Request fulfils 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 based on the Main Request filed during the oral proceedings before the board, and a description to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated