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# Datasheet for the decision of 5 October 2020

**Case Number:** T 1991/17 - 3.3.01

**Application Number:** 08765502.3

**Publication Number:** 2165716

**IPC:** A61K45/00, A61K38/00, A61P19/02, A61P19/08, A61P19/10, C07K14/705, C12Q1/02, G01N33/15, G01N33/50

**Language of the proceedings:** EN

**Title of invention:**
NOVEL BONE MASS INCREASING AGENT

**Patent Proprietor:**
Oriental Yeast Co., Ltd.

**Opponent:**
Bettenhausen, Berthold

**Headword:**
Bone mass increase by inducing osteogenesis/ORIENTAL YEAST

**Relevant legal provisions:**
EPC Art. 54, 83
RPBA 2020 Art. 13(2)

**Keyword:**

Sufficiency of disclosure - main request (no) - undue burden
Novelty - auxiliary requests 1 and 3 (no)
Admission of auxiliary requests 2 and 4 (no)

**Decisions cited:**

T 1642/06, T 0836/01, G 0002/08

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**Case Number: T 1991/17 - 3.3.01**

# D E C I S I O N
# of Technical Board of Appeal 3.3.01
# of 5 October 2020

| | |
|---|---|
| **Appellant:** (Opponent) | Bettenhausen, Berthold<br>Fasanstrasse 21<br>82223 Eichenau (DE) |
| **Representative:** | Rückerl, Florian<br>Dehmel & Bettenhausen<br>Patentanwälte PartmbB<br>Herzogspitalstraße 11<br>80331 München (DE) |
| **Respondent:** (Patent Proprietor) | Oriental Yeast Co., Ltd.<br>3-6-10, Azusawa<br>Itabashi-ku<br>Tokyo 174-8505 (JP) |
| **Representative:** | Mewburn Ellis LLP<br>Aurora Building<br>Counterslip<br>Bristol BS1 6BX (GB) |
| **Decision under appeal:** | **Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 July 2017 concerning maintenance of the European Patent No. 2165716 in amended form.** |

**Composition of the Board:**

| | |
|---|---|
| **Chairman** | A. Lindner |
| **Members:** | M. Pregetter |
| | P. de Heij |

## Summary of Facts and Submissions

I. European patent No. EP 2 165 716 was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and an inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

II. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(4) Hofbauer et al., JAMA, 2004, 292(4), 490-495

(5) Sordillo et al., Cancer (Supplement), 2003, 97(3), 802-812

(6) Kostenuik et al., Curr. Pharm. Des, 2001, 7, 613-635

(7) Body et al., Cancer (Supplement), 2003, 97(3), 887-892

(8) WO03/002713

(9) WO03/086289

(10) McClung et al., N. Engl. J. Med., 2006, 354(8), 821-831

(11) Aoki et al., J. Clin. Invest., 2006, 116(6), 1525-1534

(12) Spreafico et al., J. Cell. Biochem, 2006, 98, 1007-1020

(13) Bekker et al., J. Bone Miner. Res., 2001, 16(2), 348-360

(15) Chavassieux et al., Endocr. Rev., 2007, 28(2), 151-164

(16) D.W. Dempster, "Principles of Bone Biology", 3rd edition, Academic Press, Inc., 2008, 447-463

(17) McClung et al., N. Engl. J. Med., 2014, 370(5), 412-420

(18) Geusens, RMD Open, 2015, 1 (Suppl 1), 1-5

(19) C.J. Rosen, "Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 8th edition, John Wiley & Sons, Inc., 2013, 428-433

(30) WO2015/125922

(30b) English translation of document (30), submitted on 17 November 2017, 50 pages

(31) Chikazu et al., J. Bone Miner. Res., 2002, 17(8), 1430-1440

(32) Tamura et al., J. Bone Miner.Res., 2001, 16(10), 1772-1779

(33) Ura et al., Endocr. J., 2000, 47(3), 293-302

(34) Padhi et al., J. Bone Miner. Res., 2011, 26(1), 19-26

III. In the course of the opposition proceedings, the patent proprietor requested that the opposition be rejected and submitted auxiliary requests 1 to 9, all filed on 8 March 2017.

During the oral proceedings before the opposition division, the proprietor withdrew its main request and auxiliary requests 1 to 6. Former auxiliary request 7 was made the new main request. Former auxiliary requests 8 and 9 were renumbered 1 and 2 respectively.

IV. The opposition division came to the conclusion that the main request fulfilled the requirements of the EPC.

V. The opponent filed an appeal. It submitted document (30b).

VI. With its reply the respondent (patent proprietor) submitted auxiliary requests 1 to 3 and documents (31) to (34).

VII. The board issued a communication pursuant to Article 15(1) RPBA, identifying crucial issues in the discussion of sufficiency of disclosure and novelty.

VIII. Oral proceedings before the board took place on 5 October 2020.

In the course of the oral proceedings, the respondent filed two new auxiliary requests. The filing of new auxiliary request 2 led to renumbering of the subsequent auxiliary requests. New auxiliary request 4 replaced former auxiliary request 4 (submitted as auxiliary request 3 with the reply to the statement of grounds of appeal). Claim 1 of each of the requests in

the proceedings is reproduced below.

Claim 1 of the main request reads:
"1. A compound for use in the treatment or prevention of bone metabolic diseases associated with osteopenia by inducing osteogenesis, which is either:
(i) a compound that acts on osteoblasts or cells capable of differentiating into osteoblasts and promotes differentiation, proliferation, maturation, or calcification of osteoblasts or cells capable of differentiating into osteoblasts, wherein the compound is selected from the group consisting of:
RANK,
a variant or fragment peptide of RANK,
an anti-RANKL antibody or a functional fragment thereof; or
(ii) a peptide comprising the amino acid sequence represented by SEQ ID NO: 7 or SEQ ID NO: 16."

Claim 1 of auxiliary request 1 reads:
"1. A compound for use in the treatment or prevention of bone metabolic diseases associated with osteopenia by inducing osteogenesis, which is either:
(i) a compound that acts on osteoblasts or cells capable of differentiating into osteoblasts and promotes differentiation, proliferation, maturation, or calcification of osteoblasts or cells capable of differentiating into osteoblasts, wherein the compound is selected from the group consisting of:
RANK,
a fragment peptide of RANK,
a peptide consisting of the amino acid sequence represented by SEQ ID NO: 7 or SEQ ID NO: 16,
a fusion protein of a peptide comprising the amino acid sequence represented by SEQ ID NO: 7 or SEQ ID NO: 16 and GST or the Fc region of $IgG_1$,

an anti-RANKL antibody or a functional fragment thereof; or

(ii) a peptide comprising the amino acid sequence represented by SEQ ID NO: 7 or SEQ ID NO: 16."

Claim 1 of auxiliary request 2 (filed during oral proceedings before the board) reads:

"1. A compound for use in the treatment or prevention of bone metabolic diseases associated with osteopenia by inducing osteogenesis, which is

a compound that acts on osteoblasts or cells capable of differentiating into osteoblasts and promotes differentiation, proliferation, maturation, or calcification of osteoblasts or cells capable of differentiating into osteoblasts, wherein the compound is

an anti-RANKL antibody or a functional fragment thereof."

Claim 1 of auxiliary request 3 (filed as auxiliary request 2 with the reply to the grounds of appeal) reads:

"1. A compound for use in the treatment or prevention of bone metabolic diseases associated with osteopenia by inducing osteogenesis, which is either:

(i) a compound that acts on osteoblasts or cells capable of differentiating into osteoblasts and promotes differentiation, proliferation, maturation, or calcification of osteoblasts or cells capable of differentiating into osteoblasts, wherein the compound is selected from the group consisting of:

RANK,

a peptide consisting of the amino acid sequence represented by SEQ ID NO: 7 or SEQ ID NO: 16,

a fusion protein of a peptide comprising the amino acid sequence represented by SEQ ID NO: 7 or SEQ ID NO: 16 and GST or the Fc region of $IgG_1$,
an anti-RANKL antibody or a functional fragment thereof; or
(ii) a peptide comprising the amino acid sequence represented by SEQ ID NO: 7 or SEQ ID NO: 16."

Claim 1 of auxiliary request 4 (filed during oral proceedings before the board) reads as follows:
"1. A compound for use in the treatment or prevention of bone metabolic diseases associated with osteopenia by inducing osteogenesis, which is
a compound that acts on osteoblasts or cells capable of differentiating into osteoblasts and promotes differentiation, proliferation, maturation, or calcification of osteoblasts or cells capable of differentiating into osteoblasts, wherein the compound is
an anti-RANKL antibody or a functional fragment thereof, and wherein the ability to promote differentiation or proliferation is based on an increase in the alkaline phosphatase activity of the cells."

IX. The arguments of the appellant (opponent), insofar as they are relevant for the present decision, may be summarised as follows.

*Main request - sufficiency of disclosure*

The application as filed did not show the suitability of the claimed compounds for the claimed therapeutic application over the full scope of claim 1 of the main request. In particular, the data of the patent in suit did not provide evidence of the induction of

osteogenesis by all claimed compounds. Data on alkaline phosphatase activity were not suitable for showing that osteogenesis was induced, since no clear link between increased alkaline phosphatase activity and the treatment of osteopenia by osteogenesis had been established. Furthermore, the term "variant of RANK" (receptor activator of NF-κB) had not been defined. This term might include OPG (osteoprotegerin). It was clear from document (6) that OPG, despite its activation of alkaline phosphatase, did not lead to osteogenesis (page 619, right-hand column, paragraph 2).

*Auxiliary request 1 - novelty*

Documents (4), (5), (8), (9), (10) and (11) took away the novelty of claim 1 of auxiliary request 1. Claim 1 of auxiliary request 1 defined the disease in very broad terms. Claim 1 differed from these prior art documents merely in the term "by inducing osteogenesis". The term "by inducing osteogenesis" gave a mechanistic explanation of how the intended treatment of the disease worked. However, in the human body bone resorption and bone formation were balanced and thus closely linked (see document (6), introduction, left-hand column, or document (8), paragraph [0255]). Due to the tight link between bone resorption and bone formation, there was no way for the medical practitioner to apply the actives under consideration in a therapeutically different way. No new teaching was provided, and the clinical situation was not different from the prior art. A new mechanism of action did not automatically lead to a new clinical situation. It was to be stressed that there was no known condition of osteopenia that did not involve resorptive aspects. Some anabolic drugs were known in literature. However,

these did not interfere with the RANKL (receptor activator of NF-κB ligand) system. There was no evidence on file that an uncoupling of the signal pathways was possible within the RANKL system. To sum up, "by inducing osteogenesis" merely reflected a further mechanism of action or additional physiological effect, but did not lead per se to a new therapeutic application in the context of osteopenia.

Also the same patients were treated. The mere assertion by the patent proprietor that patients suffering from three specific diseases could benefit from the newly discovered mechanism did not change the situation. In fact, these three diseases were treated by anti-resorptive compounds in the prior art.

*Auxiliary request 2 - admission*

Auxiliary request 2 should not be admitted. Novelty had been one of the main issues throughout the opposition and appeal proceedings. There was thus no reason to submit auxiliary request 2 at this late stage of the proceedings.

*Auxiliary request 3 - novelty*

The same line of arguments applied as for auxiliary request 1.

*Auxiliary request 4 - admission*

Auxiliary request 4 should not be admitted, for the same reason as for auxiliary request 2.

X. The arguments of the respondent, insofar as they are relevant for the present decision, may be summarised as

follows.

*Main request - sufficiency of disclosure*

Alkaline phosphatase activity was well known as a marker for osteoblast activity. This was confirmed by the data in the application as filed. In addition to the *in vitro* data on alkaline phosphatase, the application as filed included *in vivo* data for peptide D (Example 11). The failure of OPG to lead to an induction of osteogenesis was an isolated failure that did not render claim 1 (which did not include OPG) insufficient. There was no undue burden to establish which compounds were fragments or variants of RANK. Document (11) provided guidance. A skilled person would look to compounds having sequence similarities, in particular since it was known that the folding of the relevant peptides was highly conserved (Figure 1 and page 1526, right-hand column, paragraph 2). A skilled person would not consider OPG to represent a variant of RANK.

*Auxiliary request 1 - novelty*

The term "by inducing osteogenesis" qualified the intended treatment. It defined how the treatment functioned. The new technical effect of inducing osteogenesis allowed patients to be treated in a new way which represented a new clinical situation. Such a new clinical situation lay in the treatment of metabolic bone disorders associated with osteopenia in which deficient osteogenesis predominated over increased bone resorption (see Table 1 of document (15)) and identified a new sub-group of patients.

In particular, this new technical effect allowed for

the treatment of patients who were not adequately treated by anti-resorptives, i.e. patients who needed more than simply the preservation of existing bone mass. According to decision T 1642/06 the group of subjects to be treated did not necessarily need to be different from that of the prior art. Moreover, no distinction between disease states was necessary.

Concerning the arguments of the appellant, the following was stated. There was a link between bone resorption and bone formation, but this homeostatic link could be disrupted under pathological conditions (see documents (15), (5), (7), (8), (10), (13) and (34)). Inhibition of bone formation was of serious concern and there existed patients in need of more than an anti-resorptive treatment (see documents (12), document (15), especially Table 1, referring to OI (osteogenesis imperfecta), Male OP (male osteoporosis) and GIOP (corticosteroid-induced osteoporosis), document (16) and post-published documents (17), (18) and (19))). The present invention broke a paradigm: it showed that uncoupling of bone resorption and bone formation was possible and that drugs that were known as anti-resorptives could be used as anabolic agents (see patent in suit, paragraph [0170]). Thus, the claimed compounds, while still having anti-resorptive properties, could be used in a new way of treatment.

*Auxiliary request 2 - admission*

Auxiliary request 2 was submitted in reaction to developments during the oral proceedings and should thus be admitted. It differed only in a deletion of subject-matter, and thus represented a simplification and removed disputed points.

*Auxiliary request 3 - novelty*

The same arguments applied as for auxiliary request 1.

*Auxiliary request 4 - admission*

In view of the fact that the opposition division had acknowledged a new clinical situation, the findings of the board represented a major change in circumstances. Auxiliary request 4 was closely related to former auxiliary request 3 (filed with the reply to the grounds of appeal), and simplified matters by deleting subject-matter that might have been problematic in the assessment of novelty.

XI. The parties' final requests were as follows.

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

The respondent requested:
-that the appeal be dismissed;
-alternatively, that the patent be maintained on the basis of the set of claims of auxiliary request 1, filed with the reply to the statement of grounds of appeal, auxiliary request 2, filed at the oral proceedings, auxiliary request 3, filed as auxiliary request 2 with the reply to the statement of grounds of appeal, or auxiliary request 4, filed at the oral proceedings.

## Reasons for the Decision

1. The appeal is admissible.

2. *Admission of documents (31) to (34)*

Documents (31) to (34) have been admitted into the proceedings. In view of the outcome of the proceedings, it is not necessary to provide reasons for their admission.

3. *Main request - sufficiency of disclosure*

3.1 Claim 1 of the main request defines compounds for use in a method referred to in Article 53(c) EPC. The definition of the compounds falling under (i) relies on a functional and a structural part.

3.2 The functional part requires that any of these compounds "acts on osteoblasts or cells capable of differentiating into osteoblasts and promotes differentiation, proliferation, maturation, or calcification of osteoblasts or cells capable of differentiating into osteoblasts".

The application as filed contains information on how to determine whether the conditions required by the functional part of the definition of the compounds are fulfilled. In paragraph [0044] (of the A publication) the increase in the alkaline phosphatase activity of the cells and the degree of calcification of the cells is mentioned. Protocols for *in vitro* tests for these two methods can be found in Examples 1 and 2.

3.3 The structural part includes references to precise structures (peptidic structure known as RANK (or fragment thereof)), compounds comprising certain amino acid sequences (SEQ ID NO: 7 or SEQ ID NO: 16), certain functionally defined structures (antibody or functional fragment thereof having a certain specificity), but also includes compounds of which the structure is merely related to a known structure in an unspecific way, i.e. "a variant of RANK".

Although the term "a variant of RANK" is disclosed in numerous passages of the application as filed, no explanation of what is to be considered a "variant" is given. No compounds representing examples of variants of RANK are listed. The term "variant of RANK" therefore includes any compound that is similar in some way (e.g. in its chemical, physical or functional properties) to RANK. The similarity need not lie in a structural similarity. The application as filed thus contains no guidance as to which compounds are "variants of RANK".

3.4 In the absence of any guidance in the application as filed as to which compounds may be considered to represent "variants of RANK", the skilled person find themselves in a position of having to necessarily resort to arbitrarily selected compounds for use in the *in vitro* tests establishing the functional requirements (see point 3.2 above).

The use of arbitrarily selected compounds in these tests amounts to trial-and-error experimentation leading to an undue burden.

Consequently, the application does not disclose the subject-matter claimed in the main request in a manner

that allows the skilled person to carry out the invention over its whole scope. The disclosure is thus insufficient (Article 83 EPC).

3.5 *Further arguments*

3.5.1 In the course of the discussion of sufficiency of disclosure, both parties made statements concerning OPG. While it was common ground that OPG did not have the required functionality, there was dispute about the classification of OPG among the compounds defined under point (i) of claim 1.
Whereas the patent in suit describes OPG, in paragraph [0022], as a protein structurally similar to RANK and binding to RANKL, the respondent argued that the skilled person would not consider OPG to be a variant of RANK. No support for this assertion was provided. Nevertheless, it follows that OPG and the analysis of its properties cannot provide any guidance as to the compounds that represent "variants of RANK".

3.5.2 The respondent has furthermore referred to document (11). This document provides the information that the folding and the receptor-ligand contact sites of members of the TNFR and TNF superfamilies are highly conserved. RANK contains key features of the TNFR(I) CRD3 contact point (page 1526, right-hand column, paragraph 2 and Figure 1). According to the respondent, this information would have provided a good starting point for the skilled person looking for variants of RANK.

The board cannot follow this argument. Document (11) cannot and does not provide a teaching for generally identifying substantially all "variants of RANK". Apart from the fact that the term "variant" includes

molecules that differ in properties other than similarities in receptor-ligand binding sites, the passage on page 1526, right-hand column, refers to molecular modelling. Molecular modelling is a complex and very specialised technique involving intimate knowledge of various parameters of the system to be modelled. In fact, it can be clearly seen from item A of Figure 1 that TNFR(I), RANK and WP9QY have conserved only 2 amino acids (Trp 107 and Ser 108) in a highlighted sequence of 5 amino acids. TNFR(I) is a peptide of 120 amino acids, RANK contains 134 amino acids and WP9QY merely 9. This shows that considerable additional input is needed to find further compounds. In the absence of any further guidance, the passage of document (11) does not lead the skilled person to "variants of RANK".

4. *Auxiliary request 1 - novelty*

4.1 The appellant has cited document (11), among other documents, as being novelty-destroying for the subject-matter of claim 1 of auxiliary request 1.

Document (11) discusses the role of WP9QY, a peptide that interferes with RANKL signalling, and its link to bone resorption and bone loss (title, abstract). Data shows that WP9QY inhibits the increased osteoclastogenesis and bone loss induced by ovariectomy or low dietary calcium in mouse models (Figure 7). Osteogenesis is not discussed in document (11).

4.2 There was agreement between the parties that WP9QY was identical to peptide D (a peptide comprising the amino acid sequence represented by SEQ ID NO: 7) and was a compound falling within the scope of claim 1 of auxiliary request 1 (and within the scope of claim 1 of

auxiliary request 3). Furthermore, it was common ground that inhibition of bone loss constituted a treatment of bone metabolic disease associated with osteopenia.

There was, however, disagreement between the parties on whether the term "by inducing osteogenesis" was suitable for establishing novelty over document (11). A closer look is thus necessary.

4.3 A new specific use of a known compound in a method of treatment of the human or animal body, which may be a use in a different treatment by therapy of the same illness, may confer novelty on a medical use claim (Article 54(5) EPC in conjunction with Article 53(c) EPC; see also G 2/08, OJ EPO 2010, 456). In the present case, the respondent has relied on two aspects that would constitute such specific use: 1) the term "by inducing osteogenesis" as a technical effect and 2) the sub-group of patients to be treated, distinguished on the basis of this technical effect.

Such aspects may potentially characterise a different, novel and inventive specific use. Therefore it has to be assessed whether these aspects are suitable for establishing such a use under the specific circumstances of the present case.

4.4 The term "by inducing osteogenesis" is thus crucial for the present decision. "By inducing osteogenesis" does not form part of the definition of the disease. Rather, this term qualifies the treatment of the disease. The question arises of whether it is to be considered a mere mechanistic explanation of the treatment, or whether this feature links the treatment to a physiological effect suitable for establishing novelty

in the context explained under point 4.3 above.

4.5 It is necessary to take a closer look at the physiological processes and mechanisms involved in the treatment of bone metabolic disease associated with osteopenia by the claimed compounds. Central to these processes and mechanisms are RANK and its ligand RANKL (patent in suit, paragraphs [0009] and [0016]).

According to the patent in suit, RANKL is a ligand for RANK. RANKL is expressed on osteoblasts or cells capable of differentiating into osteoblasts in response to stimulation by bone resorption factors (paragraph [0021]).

This can also be seen from document (4), for example. Document (4) explains that RANKL "is expressed by osteoblasts and their immature precursors and is necessary and sufficient for osteoclastogenesis. RANKL activates its receptor, RANK, which is expressed on osteoclasts and their precursors, thus promoting osteoclast formation and activation and prolonging osteoclast survival by suppressing apoptosis. RANKL is expressed on bone-forming osteoblasts, which indicates that bone resorption and bone formation are coupled through RANKL" (page 490, paragraph bridging left-hand and middle column).

The patent in suit is based on the finding that transmission of reverse signals from RANK to RANKL takes place in addition to transmission of forward signals from RANKL to RANK. The bidirectional signals transmitted between RANKL and RANK control the coupling of bone resorption and formation. By relying on the reverse signals, bone mass can be increased by bone formation (paragraph [0016]).

To sum up, agents interacting at certain points of the osteoblast-RANKL-RANK-osteoclast (or the respective precursors of these cells) signalling pathway may influence the balance (homeostasis) between bone formation and bone resorption.

4.6 The disease to be treated is defined in claim 1 of auxiliary request 1 in broad terms, referring to the physiological state (osteopenia) of the patient to be treated. Osteopenia is a condition in which bone density or bone mass is lower than normal. It includes pre-stages of more severe conditions of bone loss in which only slight changes in bone density (mass) are observed. In Claim 1 no indication is given as to pathophysiology or aetiology.

The respondent has argued that the homeostasis between bone resorption and bone formation would be disrupted under particular pathological conditions leading to a need for a treatment that targets osteogenesis rather than resorption. In this context it has cited several documents.

Document (15) explains that under normal conditions, the bone remodelling process of resorption followed by formation is closely coupled in basic multicellular units and results in no change in bone mass. The coupling between resorption and formation is controlled. Abnormalities in the rate and balance of bone remodelling play a pivotal role in the pathogenesis of bone loss and structural decay (page 154, left-hand column, last paragraph and right-hand column, first full paragraph). Table 1 lists abnormalities and identifies OI (osteogenesis imperfecta), Male OP (male osteoporosis) and GIOP

(corticosteroid-induced osteoporosis) as abnormalities showing a decrease in bone formation.

Document (5) states that, for osteopenia and osteoporosis to develop, active destruction must exceed bone formation (uncoupling of bone homeostasis) (page 808, right-hand column, last paragraph).

Document (7) describes, in the context of bone metastases, that, upon treatment with AMGN-0007, which is a recombinant OPG construct, mean BSAP (serum bone-specific alkaline phosphatase; elevated levels of BSAP indicate increased osteoblastic activity) did not decrease to the same extent as urine NTX (N-telopeptide/creatinine; elevated levels of NTX indicate increased bone resorption). BSAP decreases occurred later compared with urine NTX. This was to be expected, since bone formation and resorption are temporally coupled (page 890, right-hand column, paragraph 3).

Document (8) also confirms that bone resorption and formation are intimately linked. The active agent of document (8), αOPGL-1, leads to a decrease in bone resorption markers prior to bone formation markers (paragraph [0255]). Document (8) relates to osteopenic disorders.

Document (10) describes that the administration of denosumab to postmenopausal women with low bone mineral density leads to a decrease in bone resorption markers (serum C-telopeptide), followed with a one-month delay by a decrease in bone-specific alkaline phosphatase (a bone formation marker) (page 826, left-hand column, paragraph 3, last sentence).

Document (13) explains that administration of a single

dose of OPG to post-menopausal women rapidly decreases bone resorption. A delayed decrease in bone formation marker suggests to the authors of document (13) that OPG does not affect bone formation directly but most likely via an influence on basic multicellular units, the units responsible for bone turnover; the reason for this being that bone resorption normally precedes the coupled bone formation in the usual bone remodelling cycle (page 356, paragraph bridging the columns).

Finally, document (34) states that the most common treatments for osteoporosis are oral bisphosphonates, which act by inhibiting bone resorption. However, since bone remodelling remains coupled, a decrease in bone formation is observed (page 22, last paragraph).

From these documents it can be clearly seen that under pathological conditions bone homeostasis is disturbed. The equilibrium may be shifted towards formation or resorption, possibly due to time-related aspects. However, none of these documents reports a complete disruption of the coupling of bone formation and bone resorption.

4.7 From the paragraph above it can be seen that the term "by inducing osteogenesis" reflects certain mechanistic aspects of the RANKL signalling pathway and thus represents a physiological effect linked to the treatment of osteopenia.

In view of the disclosure of document (11), it is thus necessary to assess whether a treatment that relies on osteogenesis by influencing the RANKL signalling pathway can establish novelty over a treatment that relies on the inhibition of bone resorption involving

the same pathway.

4.7.1 A look at the mechanisms of the RANKL signalling pathway underlying the treatment is necessary. An active agent, in the present case, peptide D, is administered to a patient suffering from osteopenia. The active agent acts on its target. There seem to be two ways (see Example 11 of the patent in suit and the disclosure of document (11)), in which the agent acts: forward signalling and reverse signalling. The first way, forward signalling, leads to inhibition of bone resorption. The second way, reverse signalling, leads to osteogenesis. Both ways result in the treatment of the claimed disease. Both ways are heavily controlled in healthy subjects, and there is no indication that this control is completely lost in patients suffering from any form of osteopenia. Therefore, both ways will occur inseparably in any patient.

Consequently, the reference to "inducing osteogenesis", while indicating a physiological effect, does not lead to a situation in which forward signalling (leading to the inhibition of resorption on which document (11) relies) ceases to be of relevance.

4.7.2 The respondent has referred to two decisions of the Boards of Appeal, T 1642/06 and T 836/01.

T 1642/06 relates to the treatment of cancer by a sigma receptor ligand. The board came to the conclusion that the claimed use represented a further and different therapeutic use from that disclosed in the prior art. Whereas the prior art relied on inducing tumour cell division cycle arrest and/or apoptosis, i.e. a direct effect on tumour cells, the patent under consideration concerned an indirect influence of the active agent on

the tumour cells via the inhibition of the neovascularisation of tumours.

In T 836/01, the board found that the treatment under consideration relied on a different technical effect from the one disclosed in the prior art. Whereas the prior art disclosed the use of the active agent for the purpose of activating mature lymphoid cells exerting cytolytic T cell activity on cancer cells, i.e. an indirect effect on cancer cells, the claimed subject matter defined a direct influence on cell growth and differentiation of the cancer cells. This different effect identified a new clinical situation and related sub-group of patients.

The facts of both of these decisions differ from the present situation in that two unrelated mechanisms of action were under consideration. In contrast, the present situation concerns effects based on mechanisms of action that are closely coupled.

4.8 In conclusion, the board considers that the patent in suit provides information on a new mechanism of action of peptide D, one of the claimed compounds. This mechanism of action is closely and inseparably linked to the known activity of peptide D of inhibiting bone resorption. No evidence of complete uncoupling of these two activities has been shown. The claimed use cannot be distinguished from the known use of peptide D. The technical effect of inducing osteogenesis is therefore not apt to constitute a new specific use in the sense of point 4.3 above.

4.9 *Further arguments*

4.9.1 The respondent has argued that a treatment relying on osteogenesis allowed for the treatment of patients who were not adequately treated by anti-resorptives, i.e. patients who needed more than simply the preservation of existing bone mass. In this context it has referred to documents (12), (15), (16), (17), (18) and (19).

Document (12) explains that it is believed that dysfunctional osteoblasts are the cause of cortisone-induced osteoporosis. Therapies relying on anabolic treatment should be developed for this type of osteopenia. It goes on to state that in recent years new therapies have been proposed using drugs that could decrease the prevalence of apoptosis on osteoblasts, possibly increasing their proliferation and/or functional activity (page 1016, paragraph bridging the columns).

The relevant parts of the disclosure of document (15) can be found under point 4.6 above.

Document (16) states that bone histomorphometry has confirmed that the mechanism of action of anabolic agents is fundamentally different from that of anticatabolic drugs. Rather than reducing the activation frequency of bone remodelling, anabolic agents increase it, leading to a positive bone balance. Therefore, anabolic agents are able to improve, rather than simply preserve cancellous and cortical bone microarchitecture (paragraph bridging pages 455 and 456). The RANKL-RANK signalling pathway is not mentioned.

The post-published documents (17), (18) and (19) have no relevance for the present decision as they cannot give insight into the understanding of the skilled person at the effective date of the patent in suit, or provide evidence of how document (11) is to be read. None of these documents discusses compounds related to the RANKL-RANK signalling pathway.

It is clear from documents (12), (15) and (16) that pathophysiological situations exist in which it may be preferable to rely on an increase in bone formation for treatment. However, the actives under consideration, which are not discussed in any of these documents, will nevertheless perform their homeostatically (or at least partially) controlled functions. Thus, they cannot act as mere anabolic agents, performing only or predominantly only one of their modes/ways of action.

4.9.2 In the context of bone homeostasis and its uncoupling, the respondent has referred to paragraph [0170] of the patent in suit. There, four anti-RANKL antibodies are discussed, of which two (antibodies #22 and B) neutralise the osteoclast differentiation by RANKL, one (antibody B) having a proliferative effect on osteoblasts. Four antibodies, including antibody #22 (with no proliferative effect on osteoblasts) stimulate osteoblast differentiation, including neutralising and non-neutralising antibodies. Of two further anti-RANKL antibodies (7H12 and 10C11), one stimulates osteoblast differentiation (10C11). According to the respondent, this showed that uncoupling was possible.

The board cannot accept this argument, in particular in respect of the situation under consideration, which concerns the activity of peptide D. To begin with, bone homeostasis in the bone remodelling cycle has temporal

aspects (see documents (7), (8), (10) and (13) discussed above). It is not clear how such temporal aspects could be reflected in the experiments referred to in paragraph [0170], which were completed within a relatively short time (in relation to the bone remodelling cycle). Furthermore, paragraph [0170] deals with very specific anti-RANKL antibodies. The specific nature of the situation in paragraph [0170] is underlined by the need to differentiate between proliferative effects and the stimulation of differentiation. It is thus unclear whether these effects, and if so which ones, are relevant for peptide D.

4.9.3 To sum up, the technical effect of inducing osteogenesis is closely and inseparably linked to the known effects of the compound under consideration. In consequence, the terms "by inducing osteogenesis" cannot define the inherent presence of a new (sub) group of patients. Such a group of patients is also not explicitly mentioned in claim 1 of auxiliary request 1. Therefore, the technical effect of inducing osteogenesis is not suitable for establishing a new specific use in the treatment of osteopenia.

4.10 In view of the above, the board concludes that the subject-matter of claim 1 of auxiliary request 1 relates to the same compound for use in the same treatment of the same condition as document (11). The subject-matter of claim 1 of auxiliary request 1 lacks novelty (Article 54 EPC).

5. *Admission of auxiliary request 2*

Auxiliary request 2 was filed at a very advanced stage of the appeal proceedings, namely during the oral

proceedings before the board, after the discussion on the novelty of auxiliary request 1 had been completed. No new aspects were raised during oral proceedings before the board beyond those already addressed during the written phase of the appeal proceedings. Therefore, the filing of auxiliary request 2 cannot be seen as a timely and appropriate reaction to new developments during oral proceedings and thus as a reaction to exceptional circumstances.

The fact that claim 1 of auxiliary request 2 differs from claim 1 of auxiliary request 1 merely in the deletion of features does not change the situation. The patent proprietor is the party that is solely responsible for determining the text of the patent (see Article 113(2) EPC). It is obliged to submit amendments or possible fall-back positions. For reasons of procedural economy and fairness to the other party this must be done at the earliest possible opportunity. The nature of the amendments is not decisive for the application of Article 13(2) RPBA.

Auxiliary request 2 is not admitted into the proceedings, in accordance with Article 13(2) RPBA.

6. *Auxiliary request 3 - novelty*

Claim 1 of auxiliary request 3 lacks novelty for the same reasons as those given for claim 1 of auxiliary request 1; see point 4 above (Article 54 EPC).

7. *Admission of auxiliary request 4*

Auxiliary request 4 was filed at a very advanced stage of the appeal proceedings, namely towards the end of the oral proceedings before the board, after a

conclusion had been reached on the novelty of auxiliary request 3. No new aspects were raised during oral proceedings before the board beyond those already addressed during the written phase of the appeal proceedings. Therefore, the filing of auxiliary request 4 cannot be seen as a timely and appropriate reaction to new developments during oral proceedings and thus as a reaction to exceptional circumstances.

The fact that a board might take a different view, on the basis of arguments presented by a party, from the department whose decision is appealed does not represent exceptional circumstances as it is one of the two possibilities.

Auxiliary request 4 is not admitted into the proceedings in accordance with Article 13(2) RPBA.

## Order

## For these reasons it is decided that:

1. **The decision under appeal is set aside.**
2. **The patent is revoked.**

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated