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Datasheet for the decision of 13 September 2017

Case Number: T 0239/16 - 3.3.01

Application Number: 05012711.7

Publication Number: 1591122

IPC: A61K31/663, A61P19/08, A61P19/10

Language of the proceedings: EN

Title of invention:
Method of administering bisphosphonates

Patent Proprietors:
Novartis AG
Novartis Pharma GmbH

Opponents:
Generics [UK] Limited

Sanovel İlaç Sanayi ve Ticaret A.Ş.

Taylor Wessing LLP

Headword:
Zoledronic acid/NOVARTIS

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

Keyword:
Public availability of document (yes)
Main and auxiliary request: novelty - (yes)
Main and auxiliary request: inventive step - (no)

Decisions cited:
T 0158/96, T 1081/01, T 0715/03, T 0293/07, T 1859/08, T 1057/09, T 2506/12, T 0895/13, T 1125/13

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Case Number: T 0239/16 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 13 September 2017

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Decision under appeal:

Interlocutory decision of the Opposition Division of the European Patent Office posted on 29 January 2016 concerning maintenance of European patent No. 1591122 in amended form

Composition of the Board:

Chairman A. Lindner
Members: M. Pregetter
L. Bühler
G. Seufert
M. Blasi

Summary of Facts and Submissions

I. European patent No. 1 591 122 is based on European patent application No. 05012711.7. This is a divisional application of parent application No. 01940580.2, filed as an international application on 18 June 2001 and claiming priority from US applications No. 09/597,135 of 20 June 2000 and No. 60/267,689 of 9 February 2001.

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

(6) WO95/30421

(8) Wimalawansa et al., Bone, 1998, 23(5), abstract WG19, S648

(9) Boutsen et al., Bone, 1998, 23(5), abstract T470, S313

(10) Vasikaran et al., Bone, 1995, 17(6), 517-520

(11) Fleisch, Academic Press, 2000 Ed. 4, pages 8-11, 30-51, 128, 143-149, 152 and 181

(19) Green, BJCP Supplement, 1996, 16-18

(20) Müller et al., Drug Res., 1998, 48(1), 81-86

(26) Filipponi et al., Bone, 2000, 26(3), 269-274

(27) Hooper et al., NSW Ther. Ass. Group Inc., 2000, 1-28

(30) EP-A-275 821

(31) Lunar Corporation, "Lunar News", April 1997, 1-47

(33) Heikkinen et al., JBMR, 1997, 12(1), 103-110

(37) Extracts from trial transcripts of Hospira UK Ltd. vs Novartis AG and Generics (UK) Ltd (trading as Mylan) vs Novartis AG, HC11 E C04491 & HC 12 C02558

(38) The Pink Sheet, February 2000, 62(8), "In Brief"

(40) Khan et al., JBMR, 1997, 12(10), 1700-1707

(41) Declaration of Prof. Russell

(44) Summary of Product Characteristics (SmPC) issued by the EMA for Aclasta

(46) Miller, Clinical Therapeutics, 2005, 27(4), 361-376

(48) Mortensen et al., J. Clin. Endocrinol. Metab., 1998, 83(2), 396-402

(55) Information for the patient concerning the clinical study 42446 02 041, pages 1/6-6/6

(57) Affidavit of Prof. Leon Verbruggen

(59) Declaration of Prof. Ringe, 24 August 2015

(69a) Document relating to infringement proceedings initiated by Novartis AG et al. against Teva Pharma B.V. et al. in 2014 in France, 3 pages

(69b) Extract of Document relating to a stay of

proceedings before the Tribunal de Grande Instance de Paris, March 2016, 3 pages

(70) Reid et al., The Lancet, 1988, 1144

(71) EMEA scientific discussion (Aclasta), 1-37

(72) Second declaration of Prof. Ringe, 8 June 2016

(73) Declaration of Prof. Böger, 8 June 2016

(74) Compston, BMJ, 1994, 309, 711-715

(75) Lin, Bone, 1996, 18(2), 75-85

(76) Reginster et al., The Lancet, 1989, 1469-1471

(77) Writs of summons in France filed by Novartis AG et al.

(77a) Additional brief sheet filed by Biogaran

(89) The Pharmaceutical Codex, 12th edition, Ed. W. Lund, The Pharmaceutical Press, 1994, 342-349

(92) Declaration of Mr Fanucci, 15 March 2017

(94) Third declaration of Prof. Ringe, 4 August 2017

III. The appeals lie from the interlocutory decision of the opposition division that the patent could be maintained in amended form based on auxiliary request 1 filed during oral proceedings before the opposition division on 28 October 2015.

IV. The proprietors (Novartis AG and Novartis Pharma GmbH) and opponents 1 (Generics [UK] Ltd), 3 (Sanovel İlaç Sanayi ve Ticaret A.Ş.), 4 (Teva Pharmaceutical Industries Ltd.) and 5 (Taylor Wessing LLP) each filed notice of appeal against this decision, as well as statements of grounds of appeal. Opponent 2 (Actavis PTC ehf) did not appeal.

V. With their reply of 24 October 2016, the appellant-proprietors resubmitted the main request and auxiliary request 1 on which the decision under appeal was based. They further resubmitted auxiliary requests 2 to 7, filed during oral proceedings before the opposition division on 28 October 2015.

VI. By communication dated 17 May 2017 the board informed the parties of its decision to enlarge itself to three technically qualified members and two legally qualified members in accordance with Article 9 RPBA.

VII. Oral proceedings were held before the board on 13 September 2017. At the beginning of the oral proceedings opponent 2 withdrew its opposition and appellant-opponent 4 withdrew its opposition and its appeal. During oral proceedings the appellant-proprietors withdrew their auxiliary requests 2 to 7.

VIII. Claim 1 of the main request, filed on 24 October 2016, reads as follows:

"1. Zoledronic acid or a pharmaceutically acceptable salt thereof or any hydrate thereof for use in a method of treating osteoporosis in which the zoledronic acid or the pharmaceutically acceptable salt therefore or the hydrate thereof is administered intravenously and intermittently and in which the period between

administrations is about one year."

Claim 2 of the main request defines:

"2. A composition comprising zoledronic acid, a pharmaceutically acceptable salt thereof or any hydrate thereof for use in a method of treating osteoporosis, wherein the composition is administered intermittently and in which the period between administrations is about one year."

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request.

IX. The arguments of the appellant-proprietors which are relevant to the present decision may be summarised as follows.

Accelerated processing

With letter dated 18 August 2016, the appellant-proprietors objected to accelerated processing of the appeal. They considered that acceleration was not justified. A significant number of appeals had been filed with the board prior to the present appeal, and those should be heard first. The litigation pending in France was limited to a finding with respect to European patent No. 1 296 689, which was not the patent in suit. The case in Slovakia was not relevant, since this contracting state was not designated in European patent No. 1 296 689 and the patent in suit. Neither appellant-opponent 1 nor former appellant-opponent 4 was party to the litigation in France and Slovakia. If the parties to the national proceedings had had an

interest in the present appeal proceedings, they could have intervened pursuant to Article 105 EPC.

Admission of documents

Documents (70), (72) and (94) were not to be admitted. Document (70) could and should have been filed during opposition proceedings; it could not be seen as a reaction to the impugned decision. Document (72), filed after the statement of grounds of appeal, had been submitted without any indication of its purpose or relevance. Document (94), filed only very shortly before the oral proceedings, could not be seen either as a response to the board's communication under Article 15(1) RPBA or as a response to the previous written submissions of the appellant-proprietors. As its contents were complex, in accordance with Article 13(1) and (3) RPBA it was not to be admitted.

Public availability of document (55)

Document (55), providing information for the patient and including a patient consent form for Novartis study 42446 02 041, had not been made available to the public. It was a private document provided only to patients in the context of their possible participation in the clinical trial. The appellant-proprietors considered that there was a special relationship between the trial sponsors, the patients and the supervising doctors, although no explicit confidentiality agreement had been set up. The case law of the Boards of Appeal confirmed that there were instances where a tacit secrecy agreement applied. The present situation was similar to the one considered in decision T 1081/01. Decision T 1057/09 was also relevant in this context. The fact that document (55)

had been provided to patients asked to participate in the study could thus not be equated to the public availability of said document within the meaning of Article 54(2) EPC. Furthermore, a special relationship also existed between the patients and their family members and family doctors. There was also no evidence that a single patient had actually disclosed the content of document (55) to someone else. Document (55) had thus clearly not been made available to the public.

Novelty

Document (6) did not disclose the effective treatment of osteoporosis. It concerned distinct medical indications and mentioned osteoporosis in a very general manner by cross-referencing the treatment of osteoporosis for purposes relating to dosing.

Document (55) was merely a plan for a clinical study. The claims under consideration were medical use claims. The disclosure of document (55) could not be novelty-destroying, since the outcome of the study was not disclosed and therefore no clinical benefit either, similar to the situation in decisions T 158/96, T 1859/08 and T 2506/12. The appellant-proprietors pointed out that zoledronic acid had never been disclosed as being effective in any treatment regimen for osteoporosis.

Inventive step

Starting from document (55) the appellant-proprietors considered the technical problem to be the provision of an effective treatment with good patient compliance.

The study arm of document (55) relating to a once-yearly dosage regimen would not have been considered by the skilled person for the following reasons: There was no disclosure anywhere in the prior art that zoledronate was efficacious in any dosage for the treatment of osteoporosis in humans; animal models could provide only limited data for an effective treatment, and extrapolation from other conditions was not possible. Secondly, it was well-known in the art that it was not possible to extrapolate specific biological properties, e.g. the duration of action, from one bisphosphonate to another; and thirdly, no successful once-yearly treatment with any bisphosphonate was known for osteoporosis. Considerations involving the potency of the various bisphosphonates were mere speculation.

The appellant-proprietors stressed that it was important to consider biomarkers when assessing the actual effect of a drug at any particular point in time. Bone mineral density (BMD) had a certain lag time, both at the beginning and at the end of the treatment, and was thus only a useful indicator once a successful activity of a drug had been established.

Since there was no evidence available at the time, document (55) could merely lead to a "hope to succeed". There was no basis for a "reasonable expectation of success" in the sense that a particular dosage regimen of zoledronic acid would be expected to be continually effective, evidenced by biomarkers and BMD; reference was made to decisions T 2506/12, T 293/07, T 158/96 and T 715/03.

In addition to the line taken in these cited decisions it was also important to consider the set-up of the

study disclosed in document (55). Out of the five study arms three involved three-monthly dosing. The skilled person would thus consider that the three-monthly dosing interval was the most likely to succeed. There was no indication in document (55) that would lead the skilled person to the expectation that effective treatment would be provided in the once-yearly study arm. The once-yearly arm might have been a further control to check when the biomarkers would start to drop.

The appellant-proprietors stressed that the skilled person was not led to an expectation of success of the once-yearly study arm by the disclosure of the other documents on file. In particular, documents (11), (46), (40), (41), (31), (48), (59) and (72) were discussed. Document (11), which was a leading textbook, clearly stated that it was not possible to extrapolate from one bisphosphonate to another (page 30, last paragraph). It also described the three important aspects of the treatment, i.e. the bisphosphonate administered, the dose and the length of treatment (page 148, second paragraph). It was clear from the speculative outlook given on page 181 that the optimal regimen for the treatment of osteoporosis was not known. Document (46), post-published by several years, showed that in 2005 it was still opined that bisphosphonates differed from one another in their physiochemical and biological characteristics, which all affected the duration of action (page 363, left column, first paragraph, and page 364, right column, end of first paragraph). Moreover, the longest duration of action was considered to be six months. Document (40), an open, not controlled study, based its conclusion on questionable data sets. The passage bridging the left and middle columns on page 31 in document (31) was unfounded

speculation. The statements in expert declaration (59) were not supported by any literature. Also, the information presented in the table on page 3 of declaration (72) was inconsistent. In that table the least potent bisphosphonate could be seen to be effective over 24 months, probably due to the fact that biomarkers had not been assessed. Document (48) showed that a very potent bisphosphonate, risedronate, had a duration of action no longer than that of less potent ones. Document (41), which represented the contemporary view, clearly showed that a leading scientist was impressed and surprised by the results of the phase II study carried out by the appellant-proprietors. In summary, there was no teaching in the prior art that would lead the skilled person to the expectation that once-yearly administration would provide an effective therapeutic treatment, evidenced by biomarkers together with BMD. Consequently, the subject-matter of the main request and of auxiliary request 1 involved an inventive step.

X. The arguments of appellant-opponents 1, 3 and 5 which are relevant to the present decision may be summarised as follows.

Accelerated processing

Appellant-opponent 1 requested acceleration of the appeal proceedings on the grounds that it was seeking marketing authorisation for a zolendronic acid product and that an affiliate had been sued for infringement in France. Although the infringement proceedings were mainly based on European patent No. 1 296 689, European patent No. 1 591 122 which was the subject of the present appeal proceedings had been invoked too. Moreover, the appellant-proprietors had requested

acceleration of the opposition proceedings. In support of its request, appellant-opponent 1 filed documents (77) and (77a). Former appellant-opponent 4 also requested accelerated proceedings on the grounds that affiliates had been sued by the appellant-proprietors for infringement in France and that these affiliates had requested a stay of proceedings pending the outcome of the present appeal proceedings. In support of its request, former appellant-opponent 4 filed documents (69a) and (69b).

Admission of documents

Document (70) was filed as a reaction to the opposition division's view of the skilled person's expectation of success concerning prolonged treatment intervals. Document (72) was self-explanatory and had been discussed by the appellant-proprietors at several points in their reply to appellant-opponent 4's appeal. Document (94) was filed in response to the appellant-proprietors latest submissions.

Public availability of document (55)

There were several ways to make the contents of documents available to the public. In the present case, document (55) was given to a number of people, albeit in the context of their participation in a clinical trial, but without any explicit agreement to secrecy. The situation in respect of document (55) was therefore not a typical doctor-patient relationship. There was also no implied confidentiality, since patients taking part in the study were actively encouraged to discuss the contents of document (55) with anyone, including their families and family doctors. There could not be a breach of good faith or mutual trust if a patient did

something he had been explicitly encouraged to do (see document (57)). The confidentiality clause in document (55) was expressly limited to the sponsor having to maintain confidentiality for the collected information. There was no mention of a duty of confidentiality on the part of the patient. Also, no special situation existed for non-participating patients, to whom document (55) was also addressed, as shown in the first sentence of the document, and they also might have passed on the information contained in document (55). It was not of importance whether any of the participating patients or potentially participating patients actually disclosed the content of document (55) to anyone else; the only relevant fact was that they could have done so without violating any obligation of secrecy, and as a result they were to be considered members of the public. Furthermore, it was irrelevant whether an oral disclosure or a written disclosure had taken place. The appellant-opponents referred to page 5/6, last two paragraphs, of document (55), which clarified that copies of document (55) had been handed out. As to the cited case law, the situation in T 1081/01 was different. It was important to consider each case on its own facts.

Novelty

Document (6) individualised zoledronic acid as one of its two preferred compounds (page 5, paragraph 5). Page 6, paragraph 5, described intravenous administration as being especially preferred. The dosage regimen was disclosed on page 7, paragraph 3, where intermittent cyclical therapy once a year was described. Also, the in vivo trial in the paragraph bridging pages 2 and 3 taught intravenous administration once a year. Osteoporosis was clearly

indicated, firstly by being discussed in relation to the mechanism underlying the treatment (page 1, last paragraph) and secondly by the indication that the doses for prosthesis loosening and prosthesis migration treatment were the same as for the treatment of osteoporosis (page 7, paragraph 4). The overall disclosure of document (6) was thus that the preferred compound, zoledronic acid, given in the preferred mode of administration, intravenous, in a dosing regimen selected to be once-yearly could be used for the treatment of prosthesis loosening and in the same way for the treatment of osteoporosis.

Document (55) already disclosed all the features of the claims of the main request and of auxiliary request 1. It related to a clinical study for the treatment of osteoporosis, setting out the treatment regimen as intravenous administration of zoledronate given once yearly. Based on the general knowledge, the skilled person knew that osteoporosis would be treated to some extent in each of the study arms. Decisions T 2506/12, T 1859/08 and T 158/96 related to different circumstances. Document (89), page 342, right column, paragraph 2, stated that a clinical study was preceded by pre-clinical testing both in vitro and in animals. Many documents set out the treatment of osteoporosis with bisphosphonates and especially with zoledronic acid. Reference was made to documents (11), (19), (20), (30) and (31). Thus, although there was no evidence of the effect as such in document (55), the skilled person would have considered the effect to be present on the basis of the teaching of the prior art.

Inventive step

Starting from document (55) the distinguishing feature was the provision of the results of the clinical study. The technical problem to be solved was finding ways for the skilled person to obtain the results of the study. Alternatively, the problem could be seen as providing an effective treatment of osteoporosis. The solution was obvious. To obtain the results the skilled person would carry out the study. The study had already been designed, and there was no scientific input needed by the skilled person. The commercial burden of carrying out a clinical study did not influence the assessment of inventive step. Each treatment arm of the clinical study was technically credible. It was credible that in each arm some treatment of osteoporosis would be provided. The very inclusion of a study arm in a study led to a reasonable expectation (not certainty) of success, because clinical studies were only carried out on technically sound premises due to their being costly and time-consuming, involving patients and the associated ethical considerations. Evidence for the success of the long-term intermittent treatment of osteoporosis with zoledronic acid was robust and could be found in documents (6), (8)-(11), (27), (31), (33), (40) and (70). The appellant-opponents stressed that certainty that the effect would be achieved was not necessary, and invoked decision T 2506/12.

XI. The parties' final requests were confirmed as being as follows:

The appellant-proprietors requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the main request filed on 24 October 2016, or, alternatively,

that the appeals by the opponents 1, 3 and 5 be dismissed, i.e. the patent be maintained on the basis of auxiliary request 1 filed on 24 October 2016.

Appellant-opponents 1, 3 and 5 requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

XII. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

1. The appeals are admissible.

By respectively withdrawing their opposition and opposition/appeal, opponent 2 and appellant-opponent 4 ceased to be parties to the appeal proceedings as regards substantive issues. Other issues for which they would have remained a party to the proceedings have not arisen in the present case. In view of the further appeals that have been filed and remain pending, the present appeal proceedings are not affected by these withdrawals.

2. *Accelerated processing*

2.1 According to the Notice from the Vice-President Directorate-General 3 dated 17 March 2008 concerning accelerated processing before the boards of appeal (OJ EPO 2008, 220), parties with a legitimate interest may ask the boards of appeal to deal with their appeals rapidly. The notice mentions situations which could justify such acceleration. However, acceleration is not limited to those exemplified situations and is a matter to be decided in the discretion of the board on the

particular facts of the case before it (see e.g. decision T 895/13 and T 1125/13 of 28 March 2014, Reasons 10). While trivial reasons would clearly not justify acceleration, it follows from the scenarios exemplified in the notice that the term "legitimate interest" is not to be construed as requiring compelling reasons. Rather, objective reasons have to be put forth that warrant giving the appeal priority. Of course, the reasons invoked must be weighed against any disadvantage which might possibly ensue from granting accelerated proceedings.

2.2 In support of their requests for accelerated processing, appellant-opponent 1 and former appellant-opponent 4 argued that infringement proceedings had been brought against their affiliates in France. The board notes that these proceedings are based on an action by one of the present appellant-proprietors and its affiliates in France alleging infringement of European patent No. 1 296 689, which is not the subject of the present appeal proceedings. However, as is apparent from document (77a), the patent in suit - i.e. European patent No. 1 591 122 - has been invoked in the infringement proceedings in France (see document (77a), point 2.1). Moreover, it follows from document (69b) that a stay of the proceedings to await the decision in the present appeal proceedings was requested in March 2016. The board is thus satisfied that the present appeal proceedings have a bearing on the infringement proceedings in France. The board does not deem it appropriate for the purpose of deciding on accelerated processing to embark on a more thorough enquiry into the practical or economic impact of the present appeal proceedings on the infringement proceedings in France. Indeed, such an analysis would entail a prospective investigation into the arguments,

in the infringement proceedings, relying on the patent in suit. Such considerations would clearly exceed the scope of analysis required for deciding on a procedural request for accelerated processing.

2.3 It has not been contested that appellant-opponent 1 and former appellant-opponent 4 are not party to the infringement proceedings in France. However, it is likewise uncontested that the infringement proceedings have been brought against companies belonging to the same groups of companies as appellant-opponent 1 and former appellant-opponent 4, respectively. The board judges that this is sufficient to establish a legitimate interest within the meaning of the notice. Indeed, the notice does not establish a requirement for the parties to appeal proceedings to be party to national infringement proceedings in order to request accelerated processing. In the absence of any further argument, the board also fails to understand why a possible right of the affiliates to intervene pursuant to Article 105 EPC based on the national infringement proceedings should have a bearing on the assessment of whether appellant-opponent 1 and former appellant-opponent 4 have a legitimate interest in acceleration.

2.4 For the above reasons, the board, in the exercise of its discretion, allowed acceleration.

3. Admission of documents (70)-(76), (92) and (94)

3.1 Document (70)

Document (70), relied upon by appellant-opponents 1 and 5 immediately after appellant-opponent 4 withdrew its opposition and appeal, had been filed together with the statement setting out the grounds of appeal by the then

appellant-opponent 4. Its contents were discussed within the context of argumentation relating to the duration of action of a year or more for bisphosphonates. The duration of action was a key element of the impugned decision. Consequently, the filing of document (70) was to be seen as a legitimate attempt to strengthen appellant-opponent 4's argumentative position on this point.

In view of the above considerations, the board decided to take document (70) into account, in accordance with Article 12(1) and (4) RPBA.

3.2 Document (72)

Document (72) was filed by the then appellant-opponent 4 with the letter dated 8 June 2016, i.e. after the statement of grounds of appeal, but within four months of notification of the impugned decision. Hence, the criteria of Article 12 RPBA applied when this document was first submitted by the then appellant-opponent 4, who has not explained the reasons for the filing of document (72). Document (72) is however to some extent self-explanatory. On page 1, paragraph 3, right after the two paragraphs setting out the legitimation of Prof. Ringe to give his opinion, the intention and task of Prof. Ringe are clearly explained: "I have been asked by counsel for Teva to review the technical parts of the decision of the opposition division dated January 29, 2016." The document proceeds to set out Prof. Ringe's opinion on the connection between potency and duration of action of bisphosphonates and the relevance of biomarkers and BMD (bone mineral density) in assessing the treatment of osteoporosis. These two issues are discussed at length in the impugned decision. The board concludes that the intention behind

the filing of document (72) can be derived from the document itself and that its contents can be seen as relating directly to the impugned decision.

Consequently, document (72) was admitted into the proceedings (Article 12(1) and (4) RPBA).

3.3 Document (94)

Document (94) was filed on 14 August 2017 in a common letter on behalf of opponent 2 and the then appellant-opponent 4, i.e. about one month before the oral proceedings before the board. It is an expert declaration dealing with substantial technical issues. The last letter by the appellant-proprietors containing arguments on substantial technical points was filed on 24 October 2016. Document (94) was thus filed more than nine months after that letter and cannot be seen as a direct response to it. Nor can it be seen as a response to the board's communication under Article 15(1) RPBA, since that communication raised no substantial technical issues. Admission of the expert declaration, which was submitted at quite a late stage in the appeal proceedings by opponent 2 and then appellant-opponent 4, would have added further complexity to the case. Moreover, the board was unable to identify a change to the appellant-proprietors' case which might have justified admission of document (94) at the moment when it was presented by appellant-opponents 1 and 5 as their own.

Hence, the board decided not to admit document (94) into the proceedings (Article 13(1) RPBA).

3.4 Documents (71), (73)-(76) and (92) have not been further referred to by any of the parties. Consequently, their admission need not be discussed.

4. Public availability of document (55)

It was disputed amongst the parties whether document (55) formed part of the state of the art pursuant to Article 54(2) EPC.

Document (55) is entitled "Information for the patient concerning the study 42446 02 041". It consists of six pages numbered 1/6 to 6/6. In the introductory lines the following is stated: "Dear Madam, We would like to ask you to read the following information so that you understand the study you are asked to participate in and so that you may decide whether or not to participate... You were diagnosed with a reduced density of the bone. The medical term for this is Osteoporosis." Pages 1/6 to 3/6 give information about the objective of the study, explain the set-up of the study including details of the treatment to be given, provide information on possible benefits, risks and discomforts, and discuss contra-indications. Page 4/6 relates to other, alternative treatments, insurance conditions and confidentiality arrangements concerning patients' medical data. In the last paragraph of page 4/6 actual participation in the study is addressed. Page 5/6 relates to the information provided to the patient's general physician. The last paragraph on page 5/6 reads: "Thereafter, you must decide whether or not you would like to participate in the study. If you decide to participate, you shall be asked to sign the next page. You shall receive a photocopy of this or a second, signed copy." Finally, page 6/6 can be summarised as representing the patient consent form,

comprising statements of the patient and the physician and their signatures.

From the information that is directly obtainable from document (55) it can thus be derived that it was addressed to a number of patients suffering from osteoporosis who were asked to participate in study 42446 02 041.

Document (57) is an affidavit signed by Prof. Verbruggen. On page 2, in points 2 and 3, Prof. Verbruggen indicates that he was a clinical investigator for Novartis study 42446 02 041 and that he supervised about five patients from start to finish on the basis of a fully prepared protocol provided by the Novartis study. In point 4 he confirms that a copy of the document labelled "LV-1" annexed to his affidavit (see part of document (57) corresponding to document (55)), had been handed out to his patients. He also provided one signed version of page 6/6, with the name of the patient redacted and her signature partly removed (part of document (57), labelled "LV-2"; see point 5).

Thus, document (55) was received by patients, i.e. women suffering from osteoporosis, in the context of their participation in the study. This was not contested by the appellant-proprietors.

The essential question to be answered is therefore whether the recipients of document (55) are to be considered members of the public within the meaning of Article 54(2) EPC.

It has not been argued by the appellant-proprietors that there was an explicit confidentiality agreement

between the study sponsor and these patients or an obligation to maintain confidentiality (under national law). It remains to be seen whether there existed a special situation or some special relationship between the sponsor of the study and the patients having the consequence that the patients, as recipients of the information provided in document (55), cannot be considered members of the public due to an implied obligation to maintain confidentiality.

Of particular importance in this context is Prof. Verbruggen's affidavit (document (57)). In point 6, he stated that he had explained the contents of LV-1 to his patients and told them that, before signing the form, they should openly discuss the treatment referred to in the document with anyone, including their family and family doctor. Then he stated: "Indeed, I encouraged my patients to do so. That is without any obligation of confidentiality."

The facts given in Prof. Verbruggen's affidavit were not disputed by the appellant-proprietors, and the board sees no reason to question them. Thus, from the information that can be gained from the affidavit it is clear that his patients participating in the study were actively encouraged to discuss the contents of document (55) with "anyone".

The term "anyone" includes people who cannot be considered to be in a special relationship with the patient, let alone with the study sponsor, such as friends and other patients suffering from the same or similar conditions, as submitted by the appellant-opponents. There is thus no pointer to a special situation that would lead to the conclusion that the patients were under an implied obligation to keep the

information contained in document (55) secret. Quite to the contrary, the recipients of the information were given the impression by its donor, i.e. the study sponsor via Prof. Verbruggen, that they were free to disseminate it further without restriction. Nor was this in conflict with the information that they could derive from document (55), since the section relating to confidentiality on page 4 addressed a different issue, namely the protection of the patients' data, and there is nothing else in document (55) to suggest that particular information contained therein should be kept secret.

The decisions cited in this context by the appellant-proprietors do not further support their case. The board agrees with the principle that information cannot be regarded as made available to the public for the purpose of Article 54(2) EPC and that the recipient of that information cannot be regarded as a member of the public if at the time of receipt of the information he is in some special relationship to the donor of the information (cf. T 1081/01, Reasons 7, and T 1057/09, Reasons 5.13). However, each case has to be assessed on its own facts, and in the circumstances of the present case the board does not acknowledge the existence of such a special relationship.

It is established case law that if a single member of the public who is not under an obligation to maintain secrecy has the possibility to access particular information, this information is considered as being available to the public within the meaning of Article 54(2) EPC. In view of the fact that document (55) (or its respective country/language version, see "LV1" of document (57)) was handed out to people who were encouraged to discuss its contents with

anyone, the board comes to the conclusion that the contents of document (55) have been made available to persons neither being bound by any confidentiality agreement nor being in a special relationship to the study sponsor who are thus to be classified as members of the public.

5. Novelty

5.1 Document (6)

Document (6) relates to the use of certain methanebisphosphonic acid derivatives for the prevention and treatment of prosthesis loosening and prosthesis migration (claim 1). In the introductory part of document (6) bisphosphonates, as a class of compounds, are said to clinically inhibit excessive bone resorption in a variety of diseases, and osteoporosis is listed (page 1, last paragraph). The paragraph bridging pages 2 and 3 describes an in vivo test on sheep with unilateral hip replacement by a titanium prosthesis, but does not disclose which specific bisphosphonate is administered. On page 5, paragraphs 4 and 5, two bisphosphonates are described as especially preferred, zoledronic acid being one of them. Several administration schemes are disclosed, single doses as well as multiple doses. Multiple doses may be given either in continuous regimens or as intermittent cyclical therapy. The intermittent therapy may be effected using several intervals, e.g. once weekly, once every month, once every three months, once every six months or once a year (page 7, paragraph 3). The following paragraph, i.e. paragraph 4 on page 7, relates to doses and specifies that the doses to be administered for the therapeutic indication intended to be treated in document (6) are of the same order of

magnitude as for the treatment of, *inter alia*, osteoporosis. In summary, the disclosure of document (6) requires several selections in order to arrive at a regimen for treatment of prosthesis loosening and prosthesis migration that would, except for the medical indication, correspond to the regimen claimed in claim 1 or 2 of the main request. There is however no disclosure in document (6) of how osteoporosis is to be treated. The board agrees with the appellant-proprietors that the references to osteoporosis are background information relating to the use of bisphosphonates in general (page 1) and dosing (page 7, paragraph 4) only. Therefore, document (6) fails to disclose the subject-matter of the claims of the main request.

5.2 Document (55)

In document (55), after an introduction identifying the disease as osteoporosis and the active agent as "Zoledronate", the objective of the study is set out: "The objective of this study is to check if Zoledronate is an effective product in the prevention of bone loss in patients with post-menopausal Osteoporosis. Five different doses of Zoledronate shall be compared and it shall be determined what dose delivers the best result" (page 1/6, "Objective of the study"). The study is performed double-blindly, including a placebo arm in addition to the five study arms. From page 2/6 it can be derived that the five study arms include three arms in which different doses of zoledronate are administered at intervals of three months, one arm in which 2 mg zoledronate is administered at an interval of six months and one arm in which 4 mg zoledronate is administered at an interval of one year. The medication is injected intravenously.

The appellant-proprietors argued that the skilled person would not have expected any effective therapeutic treatment with the last study arm, i.e. the arm concerning once-yearly administration. That arm could have been included in the study for determining other effects, such as the point in time when the biomarkers start to drop. It is thus necessary for the board to carefully study document (55) to see if a conclusion can be drawn on the study sponsor's aim in including the five study arms discussed above.

In document (55) the five study arms are presented in exactly the same manner, being listed under five bullet points (page 2/6). This section of document (55) is followed, without a bullet point and thus clearly separated from said presentation, by a statement concerning the administration of the placebo. The five study arms are designed in a way that allows for data on efficacy to be obtained for different doses and for different dosing intervals. There are three study arms with different doses and three-monthly intervals, varying the dose while keeping the interval constant. The two further arms are also logically placed within the set-up of the study. Following the study arm relating to 1 mg zoledronate every three months, there is a study arm for 2 mg zoledronate every six months and a study arm for 4 mg zoledronate once a year. These arms keep the total dose administered per year constant and vary the administration frequency. From the information and the way the information is presented in document (55) the board cannot conclude that the study sponsor included any of the five arms for reasons other than studying the effectiveness of the treatment. Also, there is no indication that one study arm was considered from the outset to be unlikely to lead to a

successful therapeutic treatment. The possible and probably also actual wish of the study sponsor to observe the occurrence of certain biomarkers over time is not contradictory to this conclusion. Similar considerations apply to the post-study treatment scheme: The fact that a post-study treatment scheme comprising administration of zoledronate every three months is offered does not provide an indication that the study sponsor considered that the study arms for twice-yearly and yearly administration would fail. Each of the five study arms is equally presented and consequently seriously contemplated by the study sponsors of document (55).

In summary, it can be concluded that document (55) relates to the treatment of post-menopausal osteoporosis in human females, using, *inter alia*, 4 mg zoledronate, and administering said dose by single intravenous injection once-yearly (at the beginning of the study running for one year). There is however no disclosure of any effect, i.e. the effective treatment of osteoporosis, in document (55) itself.

In the present case the next step involves analysing whether the effect discussed above would arise with certainty from the treatment as described in document (55), i.e. whether the disclosure of document (55) has to be read as an implicit disclosure of the effective treatment of osteoporosis.

To provide support for the notion of an implicit disclosure the appellant-opponents have referred to documents (89), (11), (19), (20), (30) and (31).

Document (89) explains in the context of pharmaceutical aspects of clinical studies that administration of a

new drug to humans is preceded by extensive pre-clinical testing both in vitro and in animals (page 342, right column, paragraph 2).

Document (11) is a textbook dealing with bisphosphonates in bone disease. The actions of the bisphosphonates as a class of compounds, especially their physico-chemical and biological effects, are described on pages 34 to 51 in the context of the pre-clinical assessment of bisphosphonates. In normal animals zoledronate has been shown to have a positive effect on mechanical characteristics in various experimental osteoporosis models (page 39, first paragraph). Zoledronate is described as being among the most potent bisphosphonates (page 40 in figure 2.3-9).

Document (19) relates to the pre-clinical pharmacology of zoledronate. Zoledronate is identified as a highly potent inhibitor of bone resorption in vitro (page 16, left column, last paragraph). Results obtained from an animal model provide a basis for speculation ("may") as to the effectiveness of zoledronate in the treatment of human post-menopausal osteoporosis (page 17, left column, paragraph 2).

Document (20) discusses the effects of zoledronate on bone loss in rat models of osteopenia. A treatment time of up to 30 days was chosen ("2.3 Experimental protocol"). In the discussion part it is stated, with reference to a prior publication, that the "particular pharmacokinetic behaviour justifies intermittent administration with prolonged treatment-free intervals" (page 85, right column, paragraph 1).

Document (30) discloses substituted bisphosphonates as active agents in the treatment of, inter alia, diseases

linked to disorders in calcium metabolism, e.g. osteoporosis (claim 1, page 3, lines 21-31). Zoledronic acid is listed, among other bisphosphonates, in claim 8.

Document (31), starting on page 30, gives an update on bisphosphonates in the context of osteoporosis. On page 31 (paragraph bridging the left column and the middle column), it is suggested that high doses of a potent bisphosphonate should be given once or twice a year.

The documents cited by the appellant-opponents in this context provide no information on the use of zoledronate in humans for the treatment of osteoporosis. There is no explicit or implicit indication in any of these documents that effects of animal models or of other bisphosphonates can be directly transferred to the treatment as disclosed in document (55), i.e. to the particular dose of 4 mg, to the yearly dosing interval and to human females having post-menopausal osteoporosis. There remains a certain residual doubt that the effect, i.e. the treatment of post-menopausal osteoporosis in human females getting an intravenous dosage of 4 mg zoledronic acid once a year, is/will be achieved. Consequently, document (55) does not directly and unambiguously disclose the effective treatment of osteoporosis as defined in the independent claims of the main request.

5.3 The subject-matter of the claims of the main request is thus novel.

In the light of this conclusion it is not necessary to discuss T 2506/12, T 1859/08 and T 158/96 in this context.

6. Inventive step

6.1 The subject of the patent in suit is the therapeutic treatment of conditions of abnormally increased bone turnover, such as osteoporosis, with bisphosphonates (paragraph [0001]). The patent in suit aims at providing a convenient medicament for the treatment of osteoporosis. For this purpose the administration of a very potent N-bisphosphonate, i.e. zoledronic acid, at a very long dosing interval ([0005] and [0006]) is taught.

6.2 A possible starting point for the assessment of inventive step is document (55). The content of document (55) is discussed in detail in point 5.2 above. The five study arms are presented in the same manner. Each can be seen as a valid starting point. In the present case, the board considers the last study arm pertaining to once-yearly administration as the most promising starting point for the assessment of inventive step.

6.3 As can be seen from the discussion under point 5.2 above, the difference between the disclosure of document (55) and the subject-matter of claims 1 and 2 of the main request lies in the failure of document (55) to directly and unambiguously disclose the effective treatment of osteoporosis.

Consequently, the technical problem to be solved in view of the once-yearly arm as starting point in document (55) is the provision of an effective treatment of osteoporosis.

6.4 The board considers that the data presented in example 5 of the patent in suit provides evidence that the problem has been solved, at least for post-menopausal osteoporosis. This has not been contested by the appellant-opponents.

6.5 *Obviousness*

As already stated under point 5.2 with regard to the content of document (55) in the context of novelty, a certain doubt remains as to whether the yearly treatment arm leads to an effective treatment of osteoporosis. The question to be answered is thus whether this doubt would diminish the skilled person's expectation of success for this yearly treatment arm.

The board considers that the mere fact that an active agent selected from the group of bisphosphonates is being tested in a clinical study for the treatment of osteoporosis (as disclosed in document (55)) leads to an expectation of success, due to the fact that clinical studies are based on data obtained by pre-clinical testing both in vitro and in animals and require authority approval which takes ethical considerations into account. This means in the present case that the skilled person would expect all study arms to treat osteoporosis effectively, unless he was dissuaded from this by the prior art

Several documents have been invoked by the parties in this context. It is necessary to establish whether any of the documents cited by the parties would lead the skilled person to expect the once-yearly study arm to fail.

The contents of documents (6), (11), (19), (20), (30) and (31) have been discussed under point 5. Document (6) does not deal with the treatment of osteoporosis. The skilled person would understand from the disclosure of document (11) that the various bisphosphonates cannot be directly compared and that the results obtained with one bisphosphonate cannot be directly extrapolated to another bisphosphonate. However, the skilled person would also learn from document (11) that zoledronate is expected to act generally as a member of the group of bisphosphonates, i.e. like all other bisphosphonates zoledronate is expected to be effective in the treatment of osteoporosis. This is in line with general expectations raised by the pre-clinical studies and the studies on animal models in documents (19) and (20). Documents (30) and (31) are very general in their disclosure. However, they do not contain any indication that zoledronate would not be useful for once-yearly administration in the treatment of osteoporosis.

A brief analysis of some of the further documents needs to be carried out:

Document (8) relates to a single patient having severe osteoporosis who was successfully treated with intravenous doses of pamidronate given at six-monthly intervals. It is doubtful whether any general considerations can be derived from a study comprising a single patient.

Document (9) discusses the prevention of glucocorticoid-induced osteoporosis by intravenous administration of pamidronate. Two dosage regimens are tested, once every three months and a single dose at the beginning of the observation period of one year.

Both dosage regimens lead to primary prevention of glucocorticoid-induced osteoporosis as determined by BMD. No data on biomarkers is presented. However, indications are provided that a decrease of biomarkers was found for all groups during the first six months.

Document (10) relates to intravenous administration of alendronate and observes that the response in BMD and the majority of the tested biomarkers persisted six months after treatment (abstract, table 1).

In document (26) clodronate was tested for twice-yearly administration, and speculations are made that administration every four months may be optimal.

Document (27) is a position paper of the NSW Therapeutic Assessment Group Inc. It states, inter alia, that there is evidence to support the prevention and treatment of osteoporosis by means of four agents, namely etidronate, alendronate, pamidronate and risedronate (page 20).

Document (33) speculates that the optimum interval for etidronate and clodronate may be four times per year, based on data showing a trend toward decreasing concentrations of markers of bone turnover for up to three months.

Document (37) is a transcript of the deposition of Dr Russell before the High Court of Justice. Dr Russell states that only biomarkers give a clear picture of effective treatment, whereas BMD does not (page 443).

Document (38) reports that studies are ongoing concerning the bisphosphonate zolendronate in post-menopausal osteoporosis and corticosteroid-induced

osteoporosis (second page, last entry). There are no further details.

Document (40) reports on an open study in which alendronate was administered intravenously. Various biomarkers and BMD are assessed. The conclusion drawn in the abstract is that a sustained effect on bone turnover persists for at least one year. The appellant-proprietors questioned the data and the study set-up on which the conclusion of document (40) is based.

In document (41) Mr Russell praises the paper publishing the results of a phase II clinical study using zoledronate in the effective treatment of osteoporosis, which is the same study as described in document (55). This document does not give any indication of how Mr Russell would have judged the five study arms, especially the yearly study arm, if he had not received the results at the same time as gaining knowledge of the study set-up. The document is therefore not relevant in this context.

Document (44) is the SmPC of Aclasta and is post-published.

Document (48) relates to risedronate and includes one study arm having a cyclic treatment involving approximately two weeks of continuous treatment followed by two weeks without treatment. When the treatment was discontinued, bone turnover increased within six months toward baseline levels, and bone mass decreased significantly within one year but remained higher than in the placebo group.

Documents (59) and (72) are expert declarations filed by former appellant-opponent 4. They relate, inter

alia, to the link between potency and duration of action of specific bisphosphonates. However, the data presented, especially in document (59) under point 7 and in document (72) in the table of point 8, is not straightforward. The least potent bisphosphonate, clodronate, is presented as being effective for the longest period of time. These declarations thus cannot directly show how a skilled person presented with document (55) would have expected the once-yearly study arm to perform.

Document (70) relates to a daily dosing regimen of pamidronate and is thus not relevant.

It is not necessary to consider document (46), since it is post-published by several years. Therefore the statements it contains could not have influenced the skilled person.

To summarise, several documents assess the efficacy of therapeutic treatment with bisphosphonates, in one form or another, by assessing either biomarkers or BMD, after several months of dosing. There is no indication whatsoever in the prior art suggesting that zoledronic acid would behave differently in principle than the tested bisphosphonates. While there is no teaching in the prior art that clearly indicates that zoledronic acid is effective in the treatment of osteoporosis when given once yearly, there is on the other hand no indication either that such treatment would fail. It might even be said that in general for bisphosphonates, which also include zoledronic acid, there was speculation about persistent effects lasting at least 12 months.

The set-up of the clinical study of document (55) thus creates an expectation of success for the treatment of osteoporosis with zoledronic acid administered once yearly. That expectation is not diminished by any disclosure of the prior art. A person skilled in the art would therefore follow a dosage regimen as disclosed in document (55) for the once-yearly study arm when aiming at an effective treatment of osteoporosis and would thus arrive at the subject-matter of the independent claims of the main request.

Consequently, the subject-matter of the independent claims of the main request does not involve an inventive step (Article 56 EPC).

6.6 Further arguments

The board agrees with the appellant-proprietors that the mere fact that a clinical study is performed does not as a rule mean that the particular therapeutic effect is always achieved, in line with decision T 158/96. That decision, however, addresses novelty rather than inventive step. For the assessment of inventive step, certainty as to the outcome of a clinical study is not necessary.

The appellant-proprietors invoked decision T 293/07 in support of their argument that tests on humans are not routine approaches. The present situation, however, cannot be compared with the situation arising in case T 293/07, since document (55) already relates to human testing, whereas in T 293/07 the closest prior art relied on animal tests where ischemic incidents were produced in mice by suppressing blood flow to the brain. Also, the mode of administration varied between the claimed subject-matter (peripherally) and the

closest prior art (direct administration intraventricularly). In the present case no modifications to the teaching of the closest prior art necessitating further routine tests leading to a "try-and-see" approach are required. Unlike the situation underlying decision T 293/07, the only remaining question relates to the residual doubt as to the outcome of the clinical study of document (55).

The present situation furthermore differs from the one underlying decision T 715/03, also cited by the appellant-proprietors, in that, unlike the situation in T 715/03, animal models for osteoporosis exist and in that zoledronic acid has been successfully tested in those animal models (see document (20)). Furthermore, again unlike the situation in T 715/03, zoledronic acid belongs to the chemical class of substituted bisphosphonates, which are established drugs in the treatment of osteoporosis (see documents discussed above), whereas in T 715/03 the active agent had a chemical structure and belonged to an activity class that was remote from the active agents known to treat the disease under consideration.

The appellant-proprietors argued that, unlike the situation in case T 2506/12, in the present case there was only pre-clinical evidence that the active agent, zoledronic acid, could be effective in the treatment of osteoporosis.

The board refers to point 5.2 above, in which the fact that zoledronic acid has not yet been shown to be effective in humans is exhaustively discussed. The board holds that there remained a residual doubt that the desired treatment would be obtained, which however did not diminish the prospects of success to such an

extent that the reasonable expectation turned into a mere "hope to succeed". Clinical trials in humans are planned scientific investigations. They require authority approval, which is only given after a risk/ benefit evaluation. For ethical (but also economic) reasons it has to be ensured that research risks are minimised and are reasonable in relation to any potential benefits. Ethical and economical considerations require that the "benefit" will arise with reasonable certainty and will not only "be hoped for". This has to be taken into consideration as part of the technical circumstances when assessing the level of confidence of the skilled person in making rational predictions about achieving the envisaged treatment. Consequently, even though the circumstances are different from those of case T 2506/12, that does not automatically mean that an inventive step is to be acknowledged.

The appellant-proprietors pointed to the importance of assessing biomarkers. They explained that BMD and fracture incidences would only become of serious interest once an effective treatment had been established. The board cannot accept this argument. The three parameters under consideration, i.e. biomarkers, BMD and fracture incidences, show the effect at different levels, i.e. at the biochemical level of bone formation and resorption, at the physiological level representing the results of the biochemical processes, and finally at the clinical level corresponding to the practical aim of the treatment. Effective therapeutic treatment can be and is assessed at all three levels, as argued by the opponents and evidenced inter alia by documents (9), (10), (20), (27), (31) and (46). The board has thus taken all three parameters into account.

7. Auxiliary request 1

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request. The same conclusions as for claim 1 of the main request apply. The subject-matter of claim 1 of auxiliary request 1 is novel but does not involve an inventive step.

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