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**Datasheet for the decision
of 4 August 2009**

Case Number: T 0617/07 - 3.3.04

Application Number: 00935482.0

Publication Number: 1181318

IPC: C07K 16/28

Language of the proceedings: EN

Title of invention:

Monoclonal antibodies, synthetic and biotechnological derivatives thereof acting as NGF-antagonist molecules

Patentee:

Lay Line Genomics SpA

Opponent:

Astrazeneca UK Limited

Headword:

Monoclonal NGF-antagonist antibodies/LAY LINE

Relevant legal provisions:

EPC Art. 54, 56, 83, 123(2)(3)

Keyword:

"Added matter, extension of protection (no)"

"Sufficiency of disclosure, novelty, inventive step (yes)"

Decisions cited:

T 0226/85, T 0409/91, T 0694/92, T 0309/06

Catchword:

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Case Number: T 0617/07 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 4 August 2009

Appellant I:
(Patent Proprietor)

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Decision under appeal:

**Interlocutory decision of the Opposition
Division of the European Patent Office posted
31 January 2007 concerning maintenance of
European patent No. 1181318 in amended form.**

Composition of the Board:

Chair: U. Kinkeldey
Members: G. Alt
F. Blumer

Summary of Facts and Submissions

I. The appeals of the patent proprietor (appellant I) and the opponent (appellant II) are against the decision of the opposition division according to which European patent No. 1 181 318, entitled "Monoclonal antibodies, synthetic and biotechnological derivatives thereof acting as NGF-antagonist molecules", could be maintained in amended form pursuant to Article 102(3) EPC 1973.

II. The patent had been granted with twenty-four claims. Claims 1 to 5 and 8 to 10 as granted read:

"1. Monoclonal antibody, synthetic and biotechnological derivatives thereof, able to recognise and bind the high affinity tyrosine kinase receptor of NGF (Nerve Growth Factor), named TrkA, and act as antagonist for the binding of NGF to TrkA.

2. Monoclonal antibody, synthetic and biotechnological derivatives thereof according to claim 1 wherein the variable region of the light chain has essentially the sequence from aa. 23 to aa. 134 of SEQ ID No. 2.

3. Monoclonal antibody, synthetic and biotechnological derivatives thereof according to claim 1 wherein the variable region of the heavy chain has essentially the sequence from aa. 152 to aa. 276 of SEQ ID No. 2.

4. Monoclonal antibody, synthetic and biotechnological derivatives thereof according to any of previous claims wherein the variable region of the light chain has essentially the sequence from aa. 23 to aa. 134 of SEQ

ID No. 2 and the variable region of the heavy chain has essentially the sequence from aa. 152 to aa. 276 of SEQ ID No. 2.

5. A ScFv fragment of the monoclonal antibody according to any of previous claims comprising at least one variable region of the light chain or of the heavy chain of the antibody as described in claim 1.

8. The ScFv fragment according to claim 7 wherein said ScFv fragment has essentially the sequence of SEQ ID No. 2.

9. Synthetic or biotechnological derivative according to claim 1 comprising at least one region determining the complementarity of the antibody (CDR) and which is able to act as antagonist for the binding of NGF to TrkA.

10. Synthetic or biotechnological derivative according to claim 9 wherein said region determining the complementarity of the antibody (CDR) and which is able to act as antagonist for the binding of NGF to TrkA is within the variable region of the heavy chain from aa. 152 to aa. 276 of SEQ ID No. 2."

III. The opposition was based on Article 100(a) EPC on the grounds of lack of novelty and inventive step and on Article 100(b) EPC.

IV. In its decision the opposition division considered four requests, i.e. one main request corresponding to the claims as granted and three auxiliary requests.

Claim 1 of the first auxiliary request read:

"Monoclonal antibody, synthetic and biotechnological derivatives thereof, able to recognise and bind the high affinity tyrosine kinase receptor of NGF (Nerve Growth Factor), named TrkA, and act as antagonist for the binding of NGF to TrkA to inhibit the activity of the natural ligand being in competition with the latter for binding to the receptor itself."

Claim 1 of the second auxiliary request was the same as that of the first auxiliary request with the exception that the phrase "for use in therapy" was added at the end of the claim.

- V. The opposition division rejected the main request because claim 1 lacked novelty over the disclosure in each of documents D1, D2 and D4.

Claim 1 of the first auxiliary request was held not to be novel in view of document D2.

Claim 1 of the second auxiliary request was rejected as lacking an inventive step in view of document D6 and common general knowledge.

- VI. Finally, the claims of the third auxiliary request were held to comply with the requirements of the EPC.

Claims 1 to 5 of the third auxiliary request read as follows:

"1. Monoclonal antibody, synthetic and biotechnological derivatives thereof, able to recognise and bind the

high affinity tyrosine kinase receptor of NGF (Nerve Growth Factor), named TrkA, and act as antagonist for the binding of NGF to TrkA, wherein the variable region of the light chain has essentially the sequence from aa. 23 to aa. 134 of SEQ ID No. 2.

2. Monoclonal antibody, synthetic and biotechnological derivatives thereof, able to recognise and bind the high affinity tyrosine kinase receptor of NGF (Nerve Growth Factor), named TrkA, and act as antagonist for the binding of NGF to TrkA, wherein the variable region of the heavy chain has essentially the sequence from aa. 152 to aa. 276 of SEQ ID No. 2.

3. Monoclonal antibody, synthetic and biotechnological derivatives thereof according to any of previous claims wherein the variable region of the light chain has essentially the sequence from aa. 23 to aa. 134 of SEQ ID No. 2 and the variable region of the heavy chain has essentially the sequence from aa. 152 to aa. 276 of SEQ ID No. 2.

4. ScFv fragment of a monoclonal antibody able to recognise and bind the high affinity tyrosine kinase receptor of NGF (Nerve Growth Factor), named TrkA, and act as antagonist for the binding of NGF to TrkA, wherein said ScFv fragment has essentially the sequence of SEQ ID No. 2.

5. Synthetic or biotechnological derivative of a monoclonal antibody able to recognise and bind the high affinity tyrosine kinase receptor of NGF (Nerve Growth Factor), named TrkA, and act as antagonist for the binding of NGF to TrkA, comprising at least one region

determining the complementarity of the antibody (CDR) and which is able to act as antagonist for the binding of NGF to TrkA, wherein said region determining the complementarity of the antibody (CDR) and which is able to act as antagonist for the binding of NGF to TrkA is within the variable region of the heavy chain from aa. 152 to aa. 276 of SEQ ID No. 2."

The third auxiliary request contained fourteen further claims relating to nucleic acid encoding the antibody of claims 1 to 5, use of the nucleic acid for producing non-human transgenic animals, the non-human transgenic animals, vectors able to correctly express the nucleic acid, pharmacological compositions containing the vectors, pharmacological compositions containing the antibodies, pharmacological compositions containing the cells, and compositions of antibodies for "in-vivo" imaging diagnostics.

VII. With the statement of grounds of appeal appellant I filed a new main request corresponding to the claims as granted and auxiliary requests A to K. In a later submission auxiliary request C was replaced by a "Replacement auxiliary request C".

VIII. At the oral proceedings held before the board on 4 August 2009, appellant I filed a "New Main Request" which corresponded to the previous "Replacement auxiliary request C" and withdrew all pending auxiliary requests. The "New Main Request" had thirty-seven claims of which claims 1 to 19 corresponded to the claims of the third auxiliary request before the opposition division.

Claim 20 of the "New Main Request" read as follows:

"20. Monoclonal antibody, synthetic and biotechnological derivatives thereof, able to recognise and bind the high affinity tyrosine kinase receptor of NGF (Nerve Growth factor), named TrkA, and act as antagonist for the binding of NGF to TrkA, and which prevents the functional activation of TrkA by NGF, and characterised by at least one CDR selected from: light chain CDRs defined by aa 46-55 of SEQ ID No 2, aa 71-77 of SEQ ID No 2 and aa 110-119 of SEQ ID No 2 and heavy chain CDRs defined by aa 176-185 of SEQ ID No. 2, aa 200-216 of SEQ ID No 2 and aa 249-262 of SEQ ID No 2."

The request contained sixteen further claims all referring directly or indirectly to claim 20 and relating to single-chain fragments or synthetic or biotechnological derivatives of the antibody, nucleic acid encoding the antibody, use of the nucleic acid for producing non-human transgenic animals, the non-human transgenic animals, vectors able to correctly express the nucleic acid, pharmacological compositions containing the vectors, pharmacological compositions containing the antibodies, pharmacological compositions containing the cells, and compositions of antibodies for "in-vivo" imaging diagnostics.

Claim 37 of the "New Main Request" reads as follows:

"37. Use of a monoclonal antibody, synthetic and biotechnological derivatives thereof, able to recognise and bind the high affinity tyrosine kinase receptor of NGF (Nerve Growth Factor), named TrkA, and act as antagonist for the binding of NGF to TrkA, and which

prevents the functional activation of TrkA by NGF, in the manufacture of a pharmacological composition for the treatment of neurological pathologies comprised within the following group: chronic pain and acute pain."

IX. Appellant I requested that the decision under appeal be set aside and the case be remitted to the department of first instance with the order to maintain the patent on the basis of the New Main Request as filed during the oral proceedings before the board and a description to be adapted thereto.

Appellant II requested that the decision under appeal be set aside and that European patent No. 1 181 318 be revoked.

X. At the end of the oral proceedings the board announced its decision.

XI. The present decision refers to the following documents:

D1: The Journal of Biological Chemistry, vol. 273, no. 10, March 1998, pages 5829-5840, Urfer, R. et al.

D2: Society for Neuroscience, vol. 22, 1996, page 1010, abstract 402.11; Meeting Information: 26th annual meeting of the Society for Neuroscience, Washington D.C. USA, November 16-21, 1996; Hongo, I.S. et al.

D5: EP-A-0 471 205

D6: WO-A-95/15180

D9a: Hybridoma, vol. 14, no. 3, 1995, pages 253-259,
Hongo, J.-A. et al.

D26: Molecular Biology of the Cell, vol. 5, May 1994,
pages 549-563, Clary, D.O. et al.

D30b: Declaration of Dr. Benigni dated 3 June 2009.

XII. Appellant II's arguments, as far as they are relevant to the present decision, may be summarised as follows:

Amendments (Article 123(2) EPC)

The only antibody disclosed in the patent in relation to the function indicated in claim 37 "and which prevents the functional activation of TrkA by NGF" was the antibody MNAC13. There was no basis in the disclosure in the application as filed for linking this feature with any other antibody. Therefore, claim 37, which was not specifically directed to the antibody MNAC13, contained subject-matter extending beyond the content of the application as filed.

Clarity (Article 84 EPC)

It was not clear what exactly was meant by the expression "has essentially the sequence from ..." in claims 1 to 4 and 8.

Sufficiency of disclosure (Article 83 EPC)

Claim 20

Many of the antibodies falling under the structural definition of claim 20 would not have the functions indicated in claim 20, in particular the function "and which prevents the functional activation of TrkA by NGF". This was established by antibody HuMNACWO disclosed in declaration D30b. This antibody differed from antibody MNAC13 only in three amino acids in the third CDR of the heavy variable chain. Nevertheless, the functional profile of that antibody was not the same as that of MNAC13. It was thus to be expected that greater modifications with regard to the sequence of MNAC13 - and which were also contemplated by the structural definition in claim 20 - would lead to a complete loss of function. In the absence of any guidance, it was an undue burden for the skilled person to pick out those antibodies falling under the structural definition in claim 20 which actually had the claimed function. Thus, the disclosure in the patent was insufficient with regard to claim 20.

Claim 37

The patent only disclosed one monoclonal antibody which prevented the function of TrkA induced by NGF, i.e. MNAC13. Only with undue burden would the skilled person be able on the basis of the description and/or common general knowledge, to produce further antibodies with this functional property. This was admitted by appellant I himself in the response to the notice of opposition, where it was stated that the disclosed strategy yielded a low amount of antibody, that the strategy to obtain the antibodies was tedious and that

the isolation of antibodies with NGF-antagonist activity was a rare event and not a straightforward matter.

According to decision T 226/85 the skilled person had to have at his disposal, either in the specification or on the basis of common general knowledge, adequate information leading necessarily and directly towards success. Moreover, it was also established by the case law, such as decisions T 409/91 and T 694/92, that the protection conferred by a patent should correspond to the technical contribution to the art made by the disclosure of the invention.

Thus, since claim 37 did not specifically relate to the antibody MNAC13, the disclosure in the patent was not sufficient.

Inventive step (Article 56 EPC)

Claim 37

Each of documents D1, D2, D26 or its patent-counterpart document D6 could be considered as the closest prior art document with regard to the invention to which claim 37 related, because they all disclosed antibodies or derivatives binding to TrkA receptor. Documents D6 and D26 were particularly relevant because they disclosed an Fab-fragment preparation derived from a polyclonal antiserum directed to TrkA receptor and which Fab preparation bound to and functionally antagonized the activity of TrkA receptor. Thus, this document disclosed all elements of claim 37 except the treatment of acute and chronic pain and except that

monoclonal antibodies and its derivatives were used for the treatment. It was however known (see the introductory part of the patent, paragraphs [0007] and [0008]) that the TrkA/NGF pathway was involved in the development of pain; the preparation of monoclonal antibodies was also common general knowledge. Thus, the subject-matter of claim 37 was obvious in view of the Fab fragments taught in either of documents D6 and D26 in combination with common general knowledge.

XIII. Appellant I's arguments, as far as they are relevant to the present decision may be summarised as follows:

Amendments (Article 123(2) EPC)

Claim 37

Claim 37 and in particular the feature therein "and which prevents the functional activation of TrkA by NGF" when relating to antibodies other than MNAC13 had a basis in the application as originally filed on page 3, lines 18 to 19 and lines 27 to 28 as well as on page 4, lines 1 to 2. Therefore, claim 37 fulfilled the requirements of Article 123(2) EPC.

Clarity (Article 84 EPC)

All claims of the present request reciting the expression "has essentially the sequence from ..." were among the claims as granted. Thus, they were not open to an objection under Article 84 EPC.

Sufficiency of disclosure (Article 83 EPC)

Claim 20

The results presented in document D30b in relation to antibody HuMNACWO showed that an antibody, having - relative to the antibody MNAC13 - in particular modifications in the sequence of one of those CDRs which were the most important ones for antigen-binding, i.e. the third CDR of the heavy variable chain, had not lost the function of the parent antibody. In particular, the antibody HuMNACWO was effective in the in vivo formalin test, which was the most significant test with regard to the desired therapeutic utility, i.e. pain treatment. Therefore, it was to be expected that other changes could also be made without losing the desired functional activity.

Claim 37

The patent disclosed in a detailed way the specific method by which the antibodies disclosed in the patent, inter alia MNAC13, were obtained. Moreover, the sequence of the light and heavy chain variable regions of MNCA13 and the positions of the CDRs therein were also disclosed. This enabled the skilled person not only to produce variants of the particular antibody MNAC13 but also to produce further antibodies with the same characteristics as the antibody MNAC13, without undue burden.

Inventive step (Article 56 EPC)

Claim 37

Document D26 did not disclose a medical use of the Fab preparation derived from the polyclonal antiserum directed against TrkA receptor or the polyclonal antiserum itself. In contrast, document D6 disclosed that the anti-TrkA polyclonal antiserum could be used for treatment of pain. Pain treatment was however not disclosed in relation to the Fab preparation. Thus, the anti-TrkA polyclonal antiserum, and not the Fab preparation, had to be considered as the closest prior art. However, it was suggested by the disclosure in document D6 to treat pain by activation of TrkA receptor function and not by its inhibition as suggested by the invention. Thus, in view of document D6, the problem to be solved was the provision of an alternative treatment for pain. It was not derivable from any of the available prior art documents that the TrkA/NGF pathway was directly involved in the development of pain and therefore that the inhibition of TrkA activation was suited for pain treatment. Moreover, the disclosure in paragraphs [0007] and [0008] could not be considered as belonging to the prior art. Consequently, the subject-matter of claim 37 involved an inventive step.

Reasons for the decision

New Main Request

1. In accordance with Articles 12(2) and 13(1) of the Rules of Procedure of the Boards of Appeal, the statement of grounds of appeal is required to contain a party's complete case. Any amendments filed thereafter may be admitted at the board's discretion.

2. The New Main Request was filed at the beginning of the oral proceedings. It has 37 claims. Claims 1 to 19 and 37 correspond to claims 1 to 20 of auxiliary request D and claims 20 to 36 correspond to claims 20 to 36 of auxiliary request G, both requests having been filed with the grounds of appeal. Thus, all claims of the New Main Request had been filed with the grounds of appeal, as required by the Rules of Procedure of the Boards of Appeal cited above. Additionally, claims 1 to 19 also correspond to the claims of the third auxiliary request considered by the opposition division.

Appellant II did not object to the introduction of the New Main Request into the proceedings.

3. Therefore, the board decides to admit the "New Main Request" into the procedure.

Amendments (Articles 123(2)(3) EPC)

Extension beyond the content as filed

4. Claims 1 to 3 correspond to claims 2 to 4 as filed. Apart from the reference to other claims, which has been adapted, claim 4 corresponds to claim 8, claim 5 corresponds to claims 9 and 10, and claims 6 to 19 correspond to claim 11 to 24 as filed, respectively. Claim 20 corresponds to claim 9 as filed in combination with page 14 setting out the CDR positions within SEQ ID No. 2. Apart from the references to other claims, claims 21 to 36 correspond to claims 5 to 7, 9, 11, 14 to 24 as filed.

5. Appellant II has not raised objections pursuant to Article 123(2) EPC against any of these claims.

6. Appellant II maintains however, that claim 37, relating to monoclonal antibodies and derivatives in general (see section VIII above), had no basis in the application as filed given that the only antibody disclosed in the application as filed with the functional features recited in the claim, i.e. "able to recognise and bind the high affinity tyrosine kinase receptor of NGF (Nerve Growth Factor), named TrkA, and act as antagonist for the binding of NGF to TrkA, and which prevents the functional activation of TrkA by NGF in the manufacture of a pharmacological composition for the treatment of neurological pathologies comprised within the following group: chronic pain and acute pain" was the monoclonal antibody MNAC13.

7. In its most general terms the disclosure in the application as filed relates to monoclonal antibodies, to synthetic and biotechnological derivatives thereof, which recognise the tyrosine kinase receptor of NGF ("TrkA") and act as antagonists for the binding of NGF to Trka (page 1, lines 7 to 11). Furthermore it is disclosed that one particular monoclonal antibody which antagonises the binding of NGF to TrkA and which prevents its functional activation, namely MNAC13, reduces pain when applied to rats (page 16, "Nociception test). In the board's view, on the basis of common general knowledge and in view of the disclosure in the application as filed, the skilled person would consider that any other antibody with the same properties as those disclosed for MNAC13 in the application as filed would also be useful for the

treatment of pain. This is so because structurally different antibodies may exert the same function. The board notes that claim 37 does not require, for example, a specific affinity of interaction with the antigen, i.e. does not recite a particular feature which would prevent the skilled person from making the above extrapolation.

8. Thus, the board concludes that the subject-matter of claim 37 is derivable from the application as filed.

9. The requirements of Article 123(2) EPC are fulfilled.

Extension of protection

10. Appellant II has not raised objections pursuant to Article 123(3) EPC. Nevertheless, since the claims of the New Main Request are amended, the board examines them ex officio.

11. Independent claims 1 to 5 of the present request correspond to claims 2 to 4 and 8 to 10 as granted. Present claims 6 to 19 either directly or indirectly refer to present claims 1 to 5 and moreover correspond to claims 11 to 24 as granted.

12. In claim 20 the monoclonal antibody is defined as in claim 1 as granted and, additionally, (i) by the functional feature "which prevents the functional activation of TrkA by NGF" and (ii) by the structural feature, that it comprises a specific fragment or specific fragments of the sequence of SEQ ID No. 2. Thus, the subject-matter of claim 20 is restricted vis-à-vis that of granted claim 1 at least by the

- additional structural definition. Claims 21 to 36 either directly or indirectly refer to present claim 20 and correspond to claims 5 to 7, 9, 11 and 14 to 24 of the claims as granted.
13. Claim 37 relates to the use of monoclonal antibodies and derivatives thereof for the treatment of pain. As in claim 20 (see point 12 above), the antibodies to be used are defined by the feature "which prevents the functional activation of TrkA by NGF."
 14. In claim 1 as granted the antibodies are inter alia defined by the expression "and act as antagonist for the binding of NGF to TrkA". The meaning of this expression was an issue in the decision under appeal in the context of the evaluation of novelty, i.e. the question was whether or not the expression defines a group of antibodies that bind to TrkA and inhibit the binding of NGF to TrkA (meaning 1) or whether or not it defines a narrower group of antibodies, i.e. those that bind to TrkA, inhibit the binding of NGF to TrkA and at the same time prevent the activation of TrkA by NGF (meaning 2). The latter meaning would correspond to the explicit definition in the present claims.
 15. However, a definitive decision on the meaning of the expression in claim 1 as granted is not necessary for the board to come to a decision on whether or not claim 37 fulfils the requirements of Article 123(3) EPC. If the expression "and act as antagonist for the binding of NGF to TrkA" in claim 1 as granted was interpreted narrowly (meaning 2 above), the subject-matter of claim 37 is restricted vis-à-vis that of claim 1 as granted because the former claim is directed

to a "use" and not a "product". If the expression in claim 1 as granted is interpreted broadly (meaning 1 above), the subject-matter of claim 37 is also restricted with regard to that of claim 1 as granted, firstly because the group of antibodies to which claim 37 refers, i.e. those which prevent functional activation of TrkA by NGF, is a subgroup of the group of antibodies to which claim 1 refers, i.e. those that bind to TrkA and inhibit the binding of NGF to TrkA, and secondly because claim 37 is directed to a "use" and not a product as is claim 1 as granted.

16. In summary, it follows that the protection conferred by the claims as granted is not extended by the subject-matter of the amended claims.

17. The requirements of Article 123(3) EPC are fulfilled.

Clarity (Article 84 EPC)

18. Since Article 84 EPC is not a ground of opposition, the examination of compliance with it is restricted to amendments made over the claims as granted. The phrase "has essentially the sequence from ..." was present in claims 2 to 4, 8 and 13 as granted and is present in claims 1 to 4 and 8 of the New Main Request. The board has found above in point 11 that these claims correspond to each other. The phrase at issue is used in the same context in both sets of claims. Therefore, the phrase in claims 1 to 4 and 8 "has essentially the sequence from ..." is not open to an objection pursuant to Article 84 EPC.

19. The board has no further objections pursuant to

Article 84 EPC.

20. The requirements of Article 84 EPC are fulfilled.

Sufficiency of disclosure (Article 83 EPC)

21. Appellant II objected to sufficiency of disclosure with respect to claims 20 and 37.

Claim 20

22. Claim 20 relates to monoclonal antibodies and synthetic and biotechnological derivatives thereof. The antibodies are defined by structural and functional features (see section VIII above), i.e.

(i) they are structurally characterised in that they have "at least one CDR selected from: light chain CDRs defined by aa 46-55 of SEQ ID No 2, aa 71-77 of SEQ ID No 2 and aa 110-119 of SEQ ID No 2 and heavy chain CDRs defined by aa 176-185 of SEQ ID No 2, aa 200-216 of SEQ ID No 2 and aa 249-262 of SEQ ID No 2".

The amino acid sequences are those from the antibody characterised in the patent, MNAC13.

ii) The antibodies are furthermore functionally characterised in that they are "able to recognise and bind the high affinity tyrosine kinase receptor of NGF (Nerve Growth factor), named TrkA, and act as antagonist for the binding of NGF to TrkA, and which prevents the functional activation of TrkA by NGF".

23. Appellant II argues that it would place an undue burden on the skilled person to sort out those of the antibodies falling under the structural definition in claim 20 which actually had the claimed functions, in particular the function "which prevents the functional activation of TrkA by NGF". Consequently, the disclosure was insufficient with regard to the invention as defined in claim 20.

24. The information in the patent relating to functional variants of the specific antibody can be found in paragraph [0018] of the specification of the patent in suit, where it is stated that: "Synthetic and biotechnological derivatives of an antibody mean any engineered fragment, synthesised by chemical or recombinant techniques, which retain the functional properties of the antibody."

25. However, evaluating whether the disclosure in a patent is sufficient to enable a skilled person to carry out an invention without undue burden involves considering not only the disclosure in the patent but also the knowledge that a skilled person has from the prior art in a particular field (see for example decision T 226/85, OJ EPO 1988, 336; point 4 of the reasons).

26. The board appreciates that the provision of a functional equivalent of a particular monoclonal antibody may be a complex task. However, at the priority date of the patent in suit, on 26 May 1999, the skilled person already had extensive information about the structure of an antibody and how it is linked to its function, i.e. antigen-binding. Document D6, a patent application dealing with antibodies that mimic

the actions of neurotrophins (see the title) and having a priority date of 3 December 1993, summarises this knowledge in the introductory part on pages 13 to 31. It is inter alia disclosed that an antibody is composed of four covalently bound peptide chains, i.e. two light and two heavy chains. Each of the chains has a constant and a variable region. The variable region consists of a framework region interrupted by three hypervariable regions called complementarity-determining-regions or CDRs and which are numbered CDR1, CDR2 and CDR3. The framework regions serve to position and align the CDRs in three-dimensional space. The antigen binding site of an antibody is built from the variable regions of one heavy and one light chain. The CDRs of these chains, i.e. in toto six, are primarily responsible for binding of the antigen. (pages 13 and 14).

Document D6 also discloses that antibody variants can be designed on the basis of a specific antibody. Chimeric antibodies are for example antibodies combining the variable region of a murine antibody with the constant region of a human antibody. Another example of a chimeric antibody is a "humanized antibody", i.e. an antibody where non-human CDRs are integrated into human framework and constant regions (pages 18 to 20).

Document D6 also mentions that immunoglobulins substantially homologous to specifically described ones can be manufactured (page 28). In fact, at the priority date of the patent, the skilled person had knowledge about amino acid changes that are likely not to alter function of a protein, for example substitution of an

amino acid by a different one with similar properties, i.e. a so-called conservative substitution.

Finally, document D6 also discloses the possibility of computer-aided three-dimensional modelling of antibodies in order to reveal residues involved in antigen binding (page 31).

27. Thus, the prior art, represented by document D6, not only explains the antibody structure but also discloses a broad range of variants that can be made on the basis of a known structure of a specific antibody.
28. The board considers that, given this knowledge of the structure-function relationship of an antibody and the amino acid sequence data for six specific CDRs in claim 20, the skilled person would be able in a possibly time-consuming but straightforward manner to provide antibody variants having the functional requirements indicated in the claim.
29. In support of his argument appellant II refers to antibody HuMNACWO, disclosed in document D30b, a declaration submitted by appellant I. HuMNACWO has five CDRs in common with MNAC13, the specific antibody disclosed in the patent. The third heavy chain CDR differs from that of MNAC13 by three amino acid changes, i.e. the sequence is GAM**F**GNDF**F**F**PMDR** in HuMNACWO whereas it is GAM**Y**GNDF**F**F**Y**PMD**Y** in MNAC13.

Thus, HuMNACWO is an antibody falling under the structural definition of claim 20.

30. Document D30b discloses several assays in which HuMNACWO has been tested, such as binding to TrkA receptor as determined in an ELISA assay; binding to TrkA receptor as determined by binding to TrkA expressed on the surface of TF-1 cells and 3T3 cells as detected by cytofluorimetric analysis; surface plasmon resonance analysis to measure the binding kinetics of binding to TrkA; effect of antibodies blocking cell surface TrkA-NGFbeta mediated biological activity in a TF-1 cell proliferation assay; in vivo rat model of post-operative pain (point 7 of document D30b). It turned out that antibody HuMNACWO was not efficacious in some assay formats but was active in others, particularly the in vivo rat pain model.

Thus, in the board's view, HuMNACWO cannot be considered as an antibody that does not have the functions indicated in claim 20, and this is not argued by appellant II.

31. Rather, appellant II's argument is that, given that just a small change of three amino acids in one CDR impairs the function of the antibody when compared to MNAC13, it can be expected that even bigger structural changes like those contemplated by claim 20 would more seriously impair or even eliminate the function of the antibody. Therefore, the structural definition in claim 20 also relates to non-functional antibodies which makes a burdensome sorting out of functional antibodies necessary.

32. There is no doubt that the structural definition in claim 20 includes antibodies that do not have the desired function - the definition encompasses for

example antibodies that have only one CDR from MNAC13 - but, as noted above in point 28, when attempting to rework the invention to which claim 20 is directed the skilled person would on the basis of his/her knowledge be able to avoid non-functional variants. Therefore, because the skilled person knows how to achieve antibodies with the desired function on the basis of a particular known antibody, he/she is not in the situation of having to sort out non-functional variants in a burdensome manner.

Thus, in summary, the skilled person can rely on his/her knowledge of the art to achieve what is claimed in claim 20.

33. In view of the foregoing, the board concludes that no case of insufficiency of disclosure with regard to claim 20 has been made.

Claim 37

34. Claim 37 relates to the use of a monoclonal antibody or synthetic and biotechnological derivatives thereof in the manufacture of a pharmacological composition for the treatment of chronic and acute pain. The antibodies to be used are defined as being "able to recognise and bind the high affinity tyrosine kinase receptor of NGF (Nerve Growth Factor), named TrkA, and act as an antagonist for the binding of NGF to TrkA, and which prevents the functional activation of TrkA by NGF". The patent specifies the monoclonal antibody MNAC13 as having the indicated function.

35. In the view of appellant II the skilled person could only carry out the invention according to claim 37 with undue burden because the disclosure in the patent merely enables the skilled person to produce the exemplified antibody MNAC13.
36. However, besides the fact that the technique for making monoclonal antibodies dates from the year 1975, the patent discloses in paragraphs [0035] to [0037] in a detailed way a protocol for the production of monoclonal antibodies, which was used to prepare antibody MNAC13 and three further antibodies which inhibited binding of NGF to TrkA (paragraph [0045]). In particular, the protocol comprises the steps of immunising with cells transfected with TrkA, immunisation of different groups of mice with different concentrations of antigen-bearing cells and testing their sera for the ability to inhibit the binding of NGF to the TrkA receptor. Only splenocytes of those mice whose sera showed the greatest inhibition were used for fusion with myeloma cells.
37. According to prior-art protocols for the production of anti-TrkA antibodies available in these proceedings, the process steps carried out before splenocyte-myeloma fusion appear to be less "sophisticated". Document D1 discloses immunisation with whole antigen and the use of splenocytes of those mice with sera having the highest titer (D1 referring to "(34)", page 5830, second column, last full paragraph; reference (34) is document D9a in these proceedings, see page 254, first column, second paragraph). Documents D4 and D5 disclose immunisation with transfected cells, but no further

selection steps before fusion (D4, page 1308, second column, "Antibodies"; D5, Examples 2 and 3).

Thus, the board cannot follow appellant II's view expressed at the oral proceedings that the protocol disclosed in the patent is "normal". The board considers that the protocol according to the patent in suit has the advantage, by using specific pre-fusion selection steps, of screening for a pool of antibodies binding to TrkA and preventing NGF binding, thereby also enriching the potential pool of those antibodies which, in addition binding to TrkA and preventing NGF binding, also have the capability to prevent the activation of the TrkA receptor.

38. Thus, in the board's view, and even if it was accepted that the protocol is "normal", the patent provides the skilled person with a specific protocol making possible the preparation, in a straightforward manner, of antibodies having the function indicated in claim 37.
39. Appellant II, in its letter dated 4 June 2007, page 7, refers to submissions made by appellant I in response to the notice of opposition and argues that these statements showed that the production of antibodies functionally equivalent to MNAC13 using the process disclosed in the patent involved an undue burden. A first question arising in view of this argument - the evidential weight of statements relating to technical issues made in submissions by the parties' representatives - need not be dealt with in view of the board's finding below.

40. The statements (in the appellant I's letter of 5 August 2005) referred to by appellant II are the following:

(i)

"The very low amount of positive Mabs (4 out of 1266) renders the whole immunization strategy crucial to get the desired result." (page 3, paragraph 3).

(ii)

"The specification fully teaches how to get them, though with a long and tedious procedure" (page 4, paragraph 3).

(iii)

"d) the isolation of Mabs having the antagonist activity resulted to be a very rare event, supporting the fact that the immunization protocol is relevant to get the Mab with the desired and claimed properties;" (page 11).

(iv)

"Alternatively, one may consider that an obvious option for the skilled person was to go to the monoclonal antibody technology, as done in Annex 1 or Annex 2. However, also the disclosure of these two documents would not have fostered the expectation of the skilled person. He would have realized from the results reported therein that obtaining a Mab with a functional selective TrkA antagonist activity was not a straightforward manner." (page 12, paragraph 3).

41. In the board's view, statement (i) above means that, since the amount of positive antibodies is low, it is even more important to follow the protocol disclosed in

the patent. This point is also made in statement (iii). In the second statement it is said that the procedure is tedious, but it is also said that it is fully described in the patent and this is also the view of the board (see above point 38). As to statement (iv), Annex 1 and 2 are documents D1 and D2 in the present proceedings. None of these documents discloses or refers to an immunisation protocol which is the same as that described in the patent. Thus, this statement cannot be interpreted as saying that it was difficult to obtain monoclonal antibodies when following the protocol disclosed in the patent in suit.

42. Hence, none of these statements supports appellant II's view that the production using the process disclosed in the patent of antibodies which are functionally equivalent to MNAC13 involved an undue burden.

43. Finally, as found above, the patent also discloses in an enabling manner how functional variants of the specifically disclosed antibody MNAC13 can be made (see above points 23 to 33).

44. Thus, the board concludes that no case of lack of sufficient disclosure of claim 37 has been made.

45. Appellant II has referred inter alia to decisions T 226/85 (OJ EPO 1988, 336), T 409/91 (OJ EPO 1994, 653) and T 694/92 (OJ EPO 1997, 408) to support his case. The facts underlying these three decisions have in common with the present case that the patent or the patent application disclosed only one or very few ways of carrying out the invention. The boards in decisions T 226/85, T 409/91 and T 694/92 held that the

- disclosure of the specific examples was not sufficient to enable the invention to be carried out as claimed.
46. However, no principle can be deduced from these decisions that sufficiency of disclosure is always to be denied if there is only example of carrying out an invention. Rather it is emphasised in all three decisions that (i) the skilled person should be able to realise without undue burden substantially any embodiment falling in the ambit of a claim on the basis of the disclosure and/or common general knowledge (T 226/85, points 2 and 3; T 409/91, point 3.5, second paragraph; T 694/92, point 5, third paragraph), that (ii) the objection of lack of sufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts (T 409/91, point 3.5 second paragraph; T 694/92, point 5, third paragraph) and finally that (iii) it depends on the evidence available in each case whether or not a claimed invention can be considered as enabled on the basis of the disclosure of one worked example (T 226/85, point 5, last sentence, points 6 and 7; T 409/91, points 3.4 and 3.5, second paragraph, T 694/92, points 14 to 16).
47. The present board has balanced the facts of the present case with these considerations and has arrived at the conclusion that the requirement of sufficiency of disclosure was fulfilled with regard to claims 20 and 37 on the basis of the circumstances of the present case (see above points 36 to 44).
48. Finally, appellant II has pointed to the legal principle referred to in decisions T 409/91 and T 694/92 that patent protection should correspond to

the technical contribution disclosed in a patent. However, this is not a principle applied per se for judging whether or not the requirements of Article 83 EPC are fulfilled, as seems to be implied by appellant II's submission. Rather, it is derivable from decisions T 409/91 and T 694/92 that the aim that patent protection be fair is achieved by proper application of the requirements of the EPC.

It is stated in decision T 409/91 in point 3.5:

"[...], the underlying purpose of the requirement of support by the description, insofar as its substantive aspect is concerned, and of the requirement of sufficient disclosure is the same, namely to ensure that the patent monopoly should be justified by the actual technical contribution to the art."

Similarly, it is said in decision T 694/91 in point 3:

"This need for fair and adequate protection has been emphasised in several decisions of the boards of appeal (see, for example, T 292/85 above, and T 301/87, OJ EPO 1990, 335). The board deems it appropriate to consider the interrelation between the requirements of Articles 84, 83 and 56 EPC in order to find a fair balance in the present case."

Finally, this view is also confirmed in the more recent decision T 309/06 of 25 October 2007, point 14 of the reasons:

"All through the oral proceedings, the respondent repeatedly emphasized that claim 1 had a very wide

scope which was not commensurate with the technical contribution provided. It is undoubtedly true that the breadth of the claim is very large. However, such case law as T 19/90 (OJ EPO 1990, 476) must be remembered at this point. In this earlier case, transgenic non-human mammals were claimed on the basis of having produced transgenic mice. The then competent board decided (point 3.3 of the decision) that the mere fact that a claim is broad was not in itself a ground for considering the application as not fulfilling the requirements of sufficient disclosure under Article 83 EPC. What is of importance is whether or not the skilled person could reproduce the invention without undue burden."

49. From the foregoing the present board concludes that its finding that the disclosure is sufficient with regard to the invention in claims 20 and 37 is consistent with the earlier jurisprudence of the boards of appeal of the EPO.

50. The board has no objections with regard to the remaining claims.

51. The requirements of Article 83 EPC are fulfilled.

Novelty

52. None of the claims was objected to by appellant II for lack of novelty. The board has no objections either.

The requirements of Article 54 EPC are fulfilled.

Inventive step

53. Appellant II has not raised an objection of lack of inventive step with regard to claims 1 to 36 and the board too has no such objection. Appellant II maintains that the subject-matter of claim 37 lacks an inventive step.

The closest prior art

54. The parties considered documents D1, D2, D6 or the related scientific publication document D26 as closest prior art documents.

55. According to established case law, the primary criterion for determining the closest prior art document for assessing inventive step is that it discloses subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention. The commonality of structural features is a secondary consideration.

56. Claim 37 relates to a therapeutic application, i.e. the treatment of chronic or acute pain.

57. Document D1 discloses inter alia experiments aimed at characterising the binding site of NGF on a TrkA receptor with monoclonal antibodies. As to the physiological effect of NGF/TrkA binding, document D1 refers in the introductory part to the role of neurotrophins (NGF is a member of the neurotrophin family) in the differentiation, survival and function of neurons.

Document D2 is an abstract of a contribution at a scientific meeting. It reports on five monoclonal antibodies specific for the extracellular domains of the TrkA receptor and in particular about their epitope specificities. It is suggested that the antibodies could be valuable reagents for both in vitro and in vivo characterisation of the TrkA receptor.

Document D26 discloses a study of the effects of a polyclonal antiserum, either whole antibodies or Fab fragments, to the TrkA receptor. As far as a potential therapeutic application is concerned, document D26 refers only to the effect of NGF/TrkA binding on neuronal development (page 549, introduction).

Document D6 is the patent counterpart to document D26 and relates to the use and production of immunoglobulins which activate TrkA receptors (page 1, lines 3 to 5). In other words, it aims at producing antibodies that mimic the actions of natural TrkA ligands, such as NGF. In view of the role of NGF/TrkA in neuronal development, it is suggested on page 34 of document D6 that substances mimicking the activity of NGF can be used to treat patients with, for example, neurodegenerative disorders and thus also the pain associated with such disorders or with diabetes or chemotherapeutic treatment (page 4, lines 21-28; page 36, lines 8-12). Document D6 specifically discloses a polyclonal antiserum, RtrkA.EX (abbreviated as RTA, see page 49) that mimics the effects of NGF, i.e. it activates the TrkA receptor.

In addition, document D6 discloses a preparation of Fab fragments derived from the RTA polyclonal antiserum.

This preparation was found to inhibit TrkA receptor activation. It is suggested that the Fab preparation may be useful in the treatment of cancers such as neuroblastoma where tumour growth may depend on TrkA receptor activation (page 26, lines 16 to 28).

Finally, two classes of drugs were commonly used at the priority date of the patent in suit for treating pain, i.e. non-steroidal anti-inflammatory drugs and opiates (see for example the introductory part of the patent, paragraph [0007]).

58. It follows from the above observations that only three items among the relevant prior art are related to the purpose of the invention (which is the primary criterion for selecting the closest prior art, see point 55 above) according to claim 37, i.e. the treatment of pain, namely the non-steroidal anti-inflammatory drugs, the opiates and the polyclonal antiserum RTA disclosed in document D6.

59. Given that the polyclonal antibody preparation disclosed in document D6 is structurally (which is the secondary criterion for selecting the closest prior art, see point 55 above) closer to the monoclonal antibodies and derivatives thereof used according to claim 37, the board considers the polyclonal antibody preparation as the closest prior art.

Problem

60. Pain treatment with the polyclonal antibody preparation according to document D6 relies on activation of the TrkA receptor (see point 57 above), whereas the pain

treatment according to claim 37 relies on the inhibition of TrkA receptor activity. Therefore, the problem to be solved with regard to the closest prior art and in relation to the subject-matter of claim 37 may be formulated as the provision of an alternative way to treat pain.

Is the problem solved?

61. The patent discloses in paragraph [0058] that rats treated with the antibody MNAC13 show a significant increase of the latency of paw licking and jumping in response to temperature increase. In view of this evidence the board is satisfied that the problem formulated above has indeed been solved.

Obviousness

62. The treatment of pain according to claim 37 relies on the blocking of the TrkA receptor activity induced by NGF.
63. As observed above, pain treatment is mentioned in document D6 only in relation to activation of the TrkA receptor, whereas inactivation of the receptor is considered to be useful for cancer treatment.

Thus, the subject-matter of claim 37 is not obvious in view of the disclosure in document D6 alone.

64. As observed above in point 57, documents D1, D2 or D26 allude only to the role of TrkA/NGF binding during the development of neurons.

65. Document D5 suggests that antibodies against TrkA receptor, which is also known to be a proto-oncogen, may be used for purification of TrkA protein, in immuno-assays and for preparing a medicament for treating cancer (see claims 16 to 23).
66. Thus the subject-matter of claim 37 is not obvious in view of combination of document D6 with documents D1, D2, D5 and D26, alone or in combination.
67. At the oral proceedings the question arose in view of the summary given in the patent in paragraphs [0007] and [0008] whether or not the documents referred to in those paragraphs suggested the treatment of pain by inhibition of TrkA receptor activity. However, the two paragraphs as such were not available before the priority date. Moreover, none of the documents referred to in the two paragraphs is on file, so the board cannot ascertain whether or not their contents have been summarised such as to correctly reflect the information that the skilled person would have derived from them when reading them at the priority date of the patent. Thus, the information given in the patent in paragraphs [0007] and [0008] cannot be considered as state of the art.
68. It follows from the above that the subject-matter of claim 37 cannot be considered as obvious.
69. The requirements of Article 56 EPC are fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

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

The Registrar:

The Chair:

P. Cremona

U. Kinkeldey