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Case Number: T 0334/10 - 3.3.04

Application Number: 99938261.7

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Language of the proceedings: EN

Title of invention:
Neurotrophic growth factor

Patent Proprietor:
Janssen Pharmaceutica NV

Opponents:
Biogen Idec Inc.
NsGene A/S

Headword:
Enovin/JANSSEN PHARMACEUTICA

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2)
EPC R. 115(2)
RPBA Art. 15(3)

Keyword:
"Main request - requirements of the EPC met (yes)"

Decisions cited:
G 0002/98, T 0686/99, T 0727/00, T 0609/02, T 0464/05, T 0801/06, T 1031/06, T 1437/07, T 0107/09

Catchword:

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Case Number: T 0334/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 13 November 2014

Appellant: (Opponent 1)	Biogen Idec Inc. 14, Cambridge Center Cambridge MA 02142 (US)
Appellant: (Opponent 2)	NsGene A/S Baltorpvej 159 2750 Ballerup (DK)
Representative:	Dörries, Hans Ulrich df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Respondent: (Patent Proprietor)	Janssen Pharmaceutica NV Turnhoutseweg 30 2340 Beerse (BE)
Representative:	Boult Wade Tennant Verulam Gardens 70 Gray's Inn Road London WC1X 8BT (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 4 December 2009 concerning maintenance of the European Patent No. 1097167 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	R. Morawetz
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The appeals by opponent 1 (hereinafter "appellant I") and opponent 2 (hereinafter "appellant II") lie against the interlocutory decision of the opposition division maintaining European patent No. 1 097 167 in amended form.

II. The patent at issue has the title "Neurotrophic growth factor". It was granted in respect of European patent application No. 99938261.7, which originated from international patent application No. PCT/EP1999/005031, published as WO 00/004050 (hereinafter "application as filed").

III. Documents cited in this decision:

D2 Baloh R.H. et al., Neuron (December 1998), vol. 21, pages 1291-1302

D4 WO 00/034475

D5 US 60/111,626

D6 WO 00/18799

D9 US 09/218,698

D33 Airaksinen M.S. et al., Molecular and Cellular Neuroscience (May 1999), vol 13, pages 313-325

D34 Bennett D.L.H. et al., The Journal of Neuroscience (April 1998), vol. 18, pages 3059-3072

D35 Snider W.D. and S.B. McMahon, Neuron

April 1998), vol. 20, pages 629-632

D36 Bennett G.J., Muscle & Nerve (1993), vol. 16, pages 1040-1048

D37 Declaration of Prof. Dr. C. Sommer

D38 Hansson P., Pain (1994), vol II, issue 3, pages 1-8

D39 Postma T.J. et al., Annals of Oncology (1995), vol. 6, pages 489-494

IV. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54(3) EPC) and lack of inventive step (Article 56 EPC) and under Articles 100(b) and 100(c) EPC. The opposition division maintained the patent in amended form on the basis of auxiliary request 1.

V. The appellants filed a joint statement of grounds of appeal containing arguments under Articles 123(2), 54(3) and 83 EPC against claims 15, 17, 18 and 20 and under Article 56 EPC against claims 4, 15, 17, 18 and 20 of auxiliary request 1 as maintained by the opposition division. Documents D33 to D37 were filed with the statement of grounds of appeal.

VI. In response to the statement of grounds of appeal the proprietor (hereinafter "respondent") made auxiliary request 1 its main request and filed auxiliary requests 1 to 3. Auxiliary request 1 differed from the main request in that claim 4 had been deleted. The respondent also submitted document D38.

VII. In response the appellants maintained their objections.

VIII. The parties were summoned to oral proceedings and informed of the board's preliminary opinion in a communication pursuant to Article 15(1) RPBA.

IX. With a letter dated 10 October 2014 the respondent filed document D39, a main request and auxiliary requests 1 to 5. The main request corresponded to the previous main request, while auxiliary request 2 corresponded to previous auxiliary request 1.

X. Oral proceedings before the board took place on 12 and 13 November 2014 in the absence of the appellants, as announced in their letter of 7 November 2014. The oral proceedings were held in accordance with Rule 115(2) EPC and Article 15(3) RPBA. Documents D33 to D39 were admitted in to the proceedings. In the course of the oral proceedings the respondent filed a new main request. This request corresponded to the pending auxiliary request 2 and differed from the previous main request in the deletion of claim 4 and consequential amendments such as cross-references and claim dependencies.

Claims 14, 16, 17 and 19 of the main request read:

"14. Use of a nucleic acid molecule encoding a sequence which has at least 70% amino acid homology with the amino acid sequence of SEQ ID No.4 in the manufacture of a medicament for treating or preventing pain syndromes with a substantially peripheral or central neurogenic component.

16. Use of a nucleic acid molecule according to any of claims 1 to 4 in the manufacture of a medicament for

treating or preventing pain syndromes with a substantially peripheral or central neurogenic component.

17. Use of a neurotrophic growth factor which has at least 70% amino acid homology with the amino acid sequence of SEQ ID No.4 in the manufacture of a medicament for treating or preventing pain syndromes with a substantially peripheral or central neurogenic component.

19. Use of a neurotrophic growth factor according to any of claims 6 to 8 in the manufacture of a medicament for treating or preventing pain syndromes with a substantially peripheral or central neurogenic component."

At the end of the oral proceedings the chairwoman announced the board's decision.

XI. The arguments of the appellants submitted in writing may be summarised as follows:

Main request: claims 14, 16, 17 and 19

Amendments (Article 123(2) EPC)

The proprietor had arbitrarily picked a disease from a long list of diseases, an agent from a list of agents and a percent homology range from a list of ranges and thereby singled out an embodiment that was not disclosed in this combination in the application as filed. No hint at this combination in individualised form could be found in the application as filed (see decision T 727/00).

As to the selection of the agent: the sequence of SEQ ID NO:4 was not the preferred embodiment. It was at least plausible that amino acids 27 to 139 of SEQ ID NO:4 or even the genomic sequence of Figure 21 were the core of the invention.

As to the homology ranges: the feature "at least 70% amino acid homology" resulted from a selection from the list of sequence homologies even though the value selected was the broadest range of the list and encompassed all other disclosed ranges.

Moreover, the phrase in the paragraph on page 13, lines 3 to 11, "which are substantially homologous" pertained exclusively to the naturally occurring allelic variants and not to all variants of such sequences.

In claims 16 and 19 there was a wide choice of agents combined with a disease that was only mentioned within a large list of diseases throughout the application as filed. Selections from each of these lists were required for constructing claims 16 and 19. Original claim 24 was presumably intended to depend on original claim 23 rather than on original claim 22.

Thus, all of claims 14, 16, 17 and 19 contained subject-matter which extended beyond the content of the application as filed.

Claim interpretation

The term "pain syndromes with a substantially peripheral or central neurogenic component" was much broader than "neuropathic pain".

The ending "-pathic" indicated that the pain occurred in the course of a pathological state, whereas the term "neurogenic" simply indicated that nerves were involved in forming the pain. However, it was trivial that pain could not exist without the involvement of nerves.

Thus, the term "with a substantially peripheral or central neurogenic component" merely indicated that nerves from the peripheral or central nervous system were involved. This applied however to any pain of any origin. Accordingly, claims 14, 16, 17 and 19 simply related to the treatment of "pain syndromes" of any kind.

Sufficiency of disclosure (Article 83 EPC)

The patent's experiments with rats did not show (i) that taxol induced nerve damage upon local injection into the paw, (ii) that the animals lost sensation due to taxol, (iii) what, if they lost sensation due to taxol, exactly caused this loss and (iv) that the animals regained sensation due to reversal of nerve damage. Since it had not been shown that there was any nerve damage at all, and since it had not been shown that enovin specifically treated such nerve damage, it could not be concluded that such experiments showed a direct effect on a specific "metabolic mechanism" such as nerve damage.

The only "metabolic mechanism" that was derivable from the experiments was that taxol injection "results in an acute inflammatory reaction" (paragraph [0105]). This had nothing to do with the therapeutic application as claimed.

The experiment in the patent showed that enovin could be used for restoring sensation in cases where a loss of sensory function had occurred that might be - but not necessarily was - due to taxol administration. This did not establish a connection between the sensory function restoration effect and the relief of pain syndromes.

The experimental set-up used in the patent was unprecedented, and for this reason too the patent provided no evidence of the usefulness of enovin to treat pain.

The term "pain syndromes with a substantially peripheral or central neurogenic component" of claims 14, 16, 17 and 19 had no recognised meaning in the art. The application did not explain which conditions fell under this term, nor did it specify a test to determine whether this condition was fulfilled, nor was there any standard test to determine whether a certain pain syndrome had a "neurogenic component". Therefore, the skilled person would be at a loss when trying to establish whether he was working in the area of the claims (see decision T 464/05).

Novelty (Article 54(3) EPC)

The subject-matter of claims 14, 16, 17 and 19 enjoyed the priority date of the third priority document P3.

Document D4 and its priority document D5 described that polynucleotides encoding GRNF4 as well as GRNF4 itself might be used for "treating sensory neuropathy caused by injury to, insults to, or degeneration of, sensory neurons" or for "the treatment of peripheral sensory neuropathy or neurological disorders associated with

improperly functioning peripheral sympathetic nerves" (page 25, lines 10-16, and page 67, lines 10-12, of document D4; see also page 21, lines 19-27, and page 59, lines 11-13, of document D5). Moreover, document D4 specifically described the use of GRNF4 to treat nerve damage that occurred as a result of exposure to neurotoxins such as chemotherapeutic agents (see page 67, lines 7-9, of document D4; see also page 59, lines 8-10, of document D5). If nerve damage was treated, its side-effect pain was necessarily treated, too.

Document D6 and its priority document D9 described that polynucleotides encoding artemin as well as artemin itself might be used for treating conditions including but not limited to "peripheral neuropathy", "exposure to neurotoxins", but particularly "peripheral nerve trauma or injury" (page 34, lines 1-19, of document D6). Such nerve injuries might or might not be associated with pain, but if they were, any pain that was directly associated with the nerve injury was necessarily treated by the removal of the underlying cause, the nerve damage.

It was established case law of the Boards of Appeal that any prior art disclosure was novelty-destroying if the subject-matter claimed could be inferred directly and unambiguously from that disclosure, including features which for the skilled person were implicit in what was explicitly disclosed. This applied to the present case. It was certainly implicit in the explicit disclosure of the treatment of a medical condition (e.g. the treatment of peripheral nerve injury) that a symptom or side-effect of this condition (e.g. pain) was automatically treated by treating the underlying condition.

Thus, documents D4 and D6 anticipated the subject-matter of claims 14, 16, 17 and 19.

Inventive step (Article 56 EPC)

Document D2 disclosed mature human artemin and represented the closest prior art for the subject-matter of claims 14, 16, 17 and 19. The mature artemin protein of document D2 was 100% identical to the part of the sequence of SEQ ID NO: 4 that corresponded to mature "enovin". Document D2 further disclosed the function of artemin as a survival factor against cell death of peripheral and central neurons *in vitro* and up-regulation of the protein after peripheral nerve injury. The technical problem to be solved was to provide a medical use for artemin. Document D2 alone or in combination with documents D33, D34 or D35 rendered the claimed subject-matter obvious.

XII. The arguments of the respondent submitted in writing and during the oral proceedings may be summarised as follows:

Main request: claims 14, 16, 17 and 19

Amendments (Article 123(2) EPC)

Page 5, lines 12 to 14 and lines 21 to 26, disclosed that the most preferred nucleic acid encoding enovin was the complete sequence illustrated in Figure 1. This sequence encoded the amino acid sequence having SEQ ID NO 4. The skilled person read every passage that followed this passage on page 5 in the light of the preferred embodiment. Thus, page 11, lines 14 to 16, also referred to an isolated human neurotrophic growth factor encoded by the nucleic acid illustrated in

Figure 1, because this was the preferred nucleic acid. Page 13, line 3, related to variants of proteins of the invention and thus also to variants of the protein encoded by SEQ ID NO: 4, which was the preferred one.

The passage on page 15 in the application as filed disclosed the use of enovin for treating or preventing the listed diseases. This passage could be combined with the preferred definition of page 5.

The disclosure on page 5, lines 12 to 14 and lines 21 to 26, in conjunction with page 11, lines 14 to 16, page 13, lines 3-11, and page 15, lines 9 to 15, or page 64, lines 27 to 30, thus provided a basis for the subject-matter of present claims 14 and 17.

The 70% homology feature did not arise from a selection of mutually exclusive values. By selecting at least 70% homology the other values were not excluded from the claim but were fully encompassed therein.

The skilled person would have read the sentence on page 13, lines 3 to 7, with a comma between "variants" and "which" in line 5. Thus, the "substantially homologous" feature applied to all variants and not just to naturally occurring allelic variants. The variant tested in the examples fulfilled the "70%" feature and was not an allelic variant.

The only selection was the selection of the disease. A selection from a single list combined with other generally disclosed elements was allowable. The relevant question was whether the skilled person would contemplate combining the different features.

Claims 21, 22, 23 and 24 as filed provided a literal basis for present claims 16 and 19. Claim 24 had to be understood as referring back to claim 23 and not to claim 22.

Claim interpretation

The term "neuropathic pain" fell within the meaning of the term "neurogenic pain". "Neurogenic pain" referred to pain generated from the nervous system (see document D38) and was not just any pain syndrome.

Sufficiency of disclosure (Article 83 EPC)

The patent provided the following functional evidence: Taxol induced neuronal apoptosis (see paragraph [0089]). Enovin promoted neuronal outgrowth of staurosporine differentiated neuroblastoma cells SH-SY5Y (see paragraphs [0093] to [0095] and Figure 7). Enovin protected differentiated SH-SY5Y human neuroblastoma cells against taxol-induced cell toxicity (see Figure 6 and paragraph [0091]). Enovin reversed taxol-induced sensory dysfunction in rats and prevented taxol-induced sensory dysfunction (see Figures 19 and 20 and paragraphs [0103] to [0113]). In particular, these *in vivo* results showed a reversal and prevention of taxol-induced sensory dysfunction (see Figures 19 and 20).

The experiments with SH-SY5Y cells showed that enovin had a trophic effect on sensory neurons. The rationale for using the taxol model was that taxol was a cytotoxic anti-cancer drug, and it had been known for many years that cancer patients receiving this drug suffered peripheral neuropathy and chronic neuropathic pain as a side-effect of treatment. In other words, the

model used in the patent was based on the premise that taxol caused nerve damage and that nerve damage caused pain.

Document D39 provided evidence that neuropathy occurred as one of the toxic side-effects of taxol treatment and that nerve damage could manifest itself as pain. As shown in Table 2, higher doses of paclitaxel (taxol) caused pain in the hands and/or feet of a significant number of patients enrolled in the study, thus clearly demonstrating the link between taxol-induced neuropathy and pain. The evidence on file clearly established the link between chemotherapy, in particular with the neurotoxic drug taxol, and the development of neuropathic pain.

The rat experiments reported in the patent showed that enovin reversed and prevented taxol-induced sensory dysfunction in rats. The regained sensation was an indication of the regeneration of the nerve cells. These experiments rendered the claimed therapeutic effect plausible because it was known that cytotoxic drugs caused nerve damage and pain. Taken together, the experiments in the patent established the suitability of enovin for the claimed therapeutic application.

The sensory loss was not due to inflammation because enovin acted in a nerve-cell-specific manner.

Novelty (Article 54(3) EPC)

It was the content of the priority application of document D4, namely document D5, which was relevant for considering the novelty of the opposed claims.

The medical use claims 14, 16, 17 and 19 were all novel because document D5 did not disclose the use of GRNF4 for treating or preventing pain syndromes with a substantially peripheral or central neurogenic component. None of the data in document D5 showed any neuroprotective, neuroregenerative or trophic effects of the molecule. Thus, document D5 could not be regarded as an enabling disclosure of any medical use of GRNF4, and document D4 was hence not novelty-destroying.

For document D6 it was the content of the latest priority application, namely document D9, which was relevant for considering the novelty of the opposed claims. Document D9 was concerned with artemin polypeptides. Medical uses of these artemin polypeptides were disclosed on page 9, lines 3 to 9, page 34, lines 1 to 19, and claim 38 of document D9 and document D6. The treatment of pain syndromes with a substantially peripheral or neurogenic component was however not disclosed. Thus, document D9 could not be regarded as an enabling disclosure of any medical use of artemin, and document D6 was hence not novelty-destroying.

Inventive step (Article 56 EPC)

Document D2 showed that artemin was a novel member of the GDNF family of ligands which protected against cell death in peripheral and central neurons, was up-regulated after nerve injury and could induce differentiation in neuroblastoma cell lines.

Document D38 disclosed that antidepressants provided analgesia in a subgroup of patients with peripheral and central neurogenic pain states (see paragraph bridging

pages 4 and 5). Document D38 thus related to the same purpose as the claimed invention, while document D2 did not. Document D38 was the closest prior art document.

The problem to be solved was the provision of alternative means for the treatment of neuropathic pain. Document D2 taught that artemin could support the survival of nerve cells, but did not show that it restored nerve cell function if it was lost. There was no motivation for combining document D38 with document D2. Even if the skilled person had combined document D38 with document D2, he would have had no reasonable expectation of success. The patent showed for the first time that enovin could restore the function of nerve cells.

XIII. The appellants requested in writing that the decision under appeal be set aside and that the patent be revoked. The respondent requested that the patent be maintained on the basis of the main request filed during the oral proceedings.

Reasons for the Decision

1. The duly summoned appellants did not attend the oral proceedings, as announced in their letter of 7 November 2014. In accordance with Rule 115(2) EPC and Article 15(3) RPBA the oral proceedings took place in the absence of the appellants and they were treated as relying on their written case.

2. The patent under consideration relates to a neurotrophic growth factor, termed enovin. Enovin is also known as artemin (see documents D2, D6 and D9) or GRNF4 (see documents D4 and D5). When referring to any of these documents the board will use the nomenclature

used in the respective documents.

Main request: claims 14, 16, 17 and 19

Amendments (Article 123(2) EPC)

3. Claim 14 relates to the medical use of nucleic acid molecules encoding amino acid sequences having at least 70% amino acid homology with the amino acid sequence of SEQ ID NO:4. These compounds are to be used "in the manufacture of a medicament for treating or preventing pain syndromes with a substantially peripheral or central neurogenic component".

4. The appellants submitted that claim 14 related to subject-matter extending beyond the content of the application as filed because it was the result of the combination of elements picked randomly from at least three different lists:

(1) The protein sequence of "SEQ ID NO:4" was selected from numerous sequences covered according to the application as filed by the term "enovin";

(2) The level of homology that the variants could have in relation to SEQ ID NO:4, namely "at least 70% amino acid homology", was selected from numerous disclosed homology ranges; and

(3) The disease to be treated, namely "pain syndromes with a substantially peripheral or central neurogenic component", was selected from numerous disclosed medical indications.

5. The relevant question to be decided in assessing whether an amendment adds subject-matter extending

beyond the content of the application as filed is whether the proposed amendment is directly and unambiguously derivable from the content of the application as filed.

6. In decision T 686/99, which was followed by numerous other boards, the board held (see point 4.3.3 of the reasons) that: "(t)he content of the application as filed must not be considered to be a reservoir from which individual features pertaining to separate sections can be combined in order artificially to create a particular combination. In the absence of any pointer to that particular combination, this combined selection of features does not, for the person skilled in the art, emerge clearly and unambiguously from the content of the application as filed (cf. T 727/00 of 22 June 2001, point 1.1.4 of the reasons)."

7. In decision T 727/00 (see point 1.1.4 of the reasons) the board held that the combination of one item from each of two lists, in the absence of any pointer that supported the combination, resulted in subject-matter, which although conceptually comprised in the content of the application, could not be considered to be directly and unambiguously disclosed in this individualised form. See Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, section II.E. 1.7, for further case law in this respect.

8. In view of the appellants' arguments, the question to be answered in the present case is thus whether or not a selection from several lists occurred and, if so, whether or not the application as filed supports the selection.

9. SEQ ID NO:4

9.1 Page 5, lines 12 to 16, of the application as filed discloses that:

> "[a]ccording to a first aspect of the present invention there is provided a nucleic acid molecule encoding a human neurotrophic growth factor, designated herein as enovin, having the amino acid sequence illustrated in Figure 21, or encoding a functional equivalent, derivative or bioprecursor of said growth factor."

Pursuant to page 5, lines 21 to 26, of the application as filed:

> "[p]referably, the nucleic acid according to the invention comprises the sequence from positions 81 to 419 of the sequence illustrated in Figure 1 and more preferably from positions 81 to 422 and even more preferably the complete sequence illustrated in Figure 1."

9.2 It was undisputed that the complete sequence illustrated in Figure 1 encodes the amino acid sequence of SEQ ID NO:4. Thus, page 5 discloses to the skilled person that the most preferred nucleic acid encoding enovin is the complete sequence illustrated in Figure 1, which sequence encodes the amino acid sequence depicted in SEQ ID NO: 4.

9.3 In view of the disclosure on page 5, the appellants' submission that it was at least plausible that not the entire sequence of SEQ ID NO: 4 was the preferred embodiment but that amino acids 27 to 139 of SEQ ID NO:4 or even the genomic sequence of Figure 21

constituted the core of the invention is not considered persuasive.

10. Variants with at least 70% amino acid homology

10.1 The paragraph on page 13, lines 3 to 11, of the application as filed discloses that:

> "[p]roteins or polypeptides according to the invention further include variants of such sequences, including naturally occurring allelic variants which are substantially homologous to said proteins or polypeptides. In this context, substantial homology is regarded as a sequence which has at least 70%, and preferably 80%, 90% or 95% amino acid homology with the proteins or polypeptides encoded by the nucleic acid molecule according to the invention."

The skilled person would consider the information content of this paragraph with the disclosure of page 5 in mind, namely that the most preferred nucleic acid encoding enovin encodes the amino acid sequence depicted in SEQ ID NO:4. In the board's view the skilled person would thus understand that the invention encompasses in particular variants of enovin having SEQ ID NO:4.

10.2 The passage from page 13 cited in point 10.1 above defines the relationship of the variants with the most preferred "parent" sequence in terms of homology. The appellants submitted in this context that the phrase "which are substantially homologous" pertained exclusively to the naturally occurring allelic variants and not to all variants of such sequences as claimed in claim 14, which claim therefore contained added

subject-matter.

10.3 In the board's view, the skilled person would not interpret the passage as suggested by the appellants because he would find it implausible that only the subgroup of the allelic variants was defined by the homology to the "parent" sequence, but not other types of variants. Thus, the skilled person - inferring a comma between the words "variants" and "which" - would have related the phrase "which are substantially homologous" to all variants, including the naturally occurring allelic variants. This understanding of the passage on page 13 is supported by the example which discloses a variant of SEQ ID NO:4 which has at least 70% homology with SEQ ID NO:4 but is not a naturally occurring allelic variant thereof.

10.4 In the context of the passage from page 13, cited in point 10.1 above, the appellants further submitted that the feature in claims 14 and 17 "at least 70% amino acid homology" resulted from a selection from the list of sequence homologies recited in this passage. However, the homology ranges disclosed in this passage are not mutually exclusive values. Indeed, the range of "at least 70% amino acid homology" referred to in claim 14 represents the largest range which encompasses all the other ranges, such that no "selection" has occurred. Indeed, the choice of "at least 70% amino acid homology" does not result in the skilled person being presented with new technical information.

10.5 The board concludes from points 9 to 10.4 above that the application as filed discloses on page 5 in combination with page 13 that the preferred nucleic acid encoding enovin is a nucleic acid molecule encoding a sequence which has at least 70% amino acid

homology with the amino acid sequence of SEQ ID NO:4. The application as filed therefore provides a clear pointer motivating the skilled person to choose these enovin sequences out of all enovin sequences disclosed in the application as filed.

11. The disease to be treated: "pain syndromes with a substantially peripheral or central neurogenic component"

11.1 The disease to be treated as referred to in the claim at issue is "pain syndromes with a substantially peripheral or central neurogenic component". The appellants argue that this disease was arbitrarily picked from an extensive list of diseases disclosed in three paragraphs on pages 14 to 15 of the application as filed.

11.2 Pages 14 and 15 do indeed recite numerous diseases. However, while the first two paragraphs on pages 14 to 15 propose various medical treatments based on the sequence similarity of enovin and known growth factors or unspecified observations, the third paragraph discloses that the data obtained in the examples of the application led to the identification of enovin as a candidate for the treatments proposed in this paragraph. This sets these treatments apart from the remaining treatments. The passage on page 15 reads:

> "Additionally, and which is described in more details in the example below, enovin has been shown to speed up recovery of induced sensory deficits, which identifies enovin as a candidate for treating or alleviating pain syndromes with a peripheral or central neurogenic component, rheumatic/inflammatory diseases as

well as conductance disturbances, by administration to a patient in need thereof in sufficient concentration to reduce or prevent the symptoms of these disorders."

11.3 In the board's view, the skilled person, considering that the term "enovin" is used in the application to describe different molecules including the most preferred one (see paragraph 10.5 above), would directly and unambiguously conclude that the compounds as identified in point 10.5 above are to be used for the treatment of any of the three disorders, one of them being "pain syndromes with a substantially peripheral or central neurogenic component".

12. The board concludes from points 9 to 11.3 above that the only selection required in order to arrive at the subject-matter of claim 14 is the selection of the disease to be treated from the list of three indications disclosed in the passage on page 15 (see point 11.2 above). A single selection of an element from a list does not create any new technical information.

13. In view of the observations in points 9 to 12 above the board cannot accept that, as argued by the appellants, the combination of features in claim 1 is the result of a selection of elements picked randomly from three different lists. The subject-matter of claim 14 does not extend beyond the content of the application as filed.

14. The same conclusion applies *mutatis mutandis* to the subject-matter of claim 17, which relates to the use of a neurotrophic growth factor which has at least 70% amino acid homology with the amino acid sequence of

SEQ ID NO:4 in the manufacture of a medicament for treating or preventing pain syndromes with a substantially peripheral or central neurogenic component.

15. Claim 16 relates to the use of a nucleic acid molecule according to any of claims 1 to 4 in the manufacture of a medicament for treating or preventing pain syndromes with a substantially peripheral or central neurogenic component.

16. Claim 21 as filed discloses the "[u]se of a nucleic acid molecule according to any of claims 1 to 6 in the manufacture of a medicament for treating or preventing neural disorders in a subject", and claim 22 as filed further defines the neural disorder as being selected from a group comprising *inter alia* "pain syndromes with a substantially peripheral or central neurogenic component". Claims 21 and 22 as filed thus provide a literal basis for present claim 16, and the only selection that was made in arriving at the subject-matter of present claim 16 is the selection of the disease.

17. An analogous line of argument applies to the subject-matter of claim 19, which is based on claims 23 and 24 as filed. The board notes in this regard that the appellants accepted that claim 24 as filed was presumably intended to depend on claim 23 as filed rather than on claim 22 as filed.

18. For the reasons indicated above the board decides that the main request complies with the requirements of Article 100(c) EPC and Article 123(2) EPC.

Claim interpretation

19. The appellants submitted that the term "with a substantially peripheral or central neurogenic component" merely indicated that nerves from the peripheral or central nervous system were involved and that claims 14, 16, 17 and 19 thus related to the treatment of "pain syndromes" of any cause.

20. However, pursuant to document D38 (see abstract), peripheral neurogenic pain may follow transient pressure upon or stretching of a peripheral nerve or root, or reflect sustained damage to a nerve ("neuropathic pain") such as in polyneuropathy or entrapment neuropathy or after herpes zoster. Alternatively, neurogenic pain may have a central origin such as stroke, multiple sclerosis or trauma, especially of the spinal cord. The board thus considers that the skilled person would understand the term "pain syndromes with a substantially peripheral or central neurogenic component" as describing pain which arises from the nervous system itself and not just any pain.

Sufficiency of disclosure (Article 83 EPC)

21. Pursuant to established case law of the Boards of Appeal for a medical use claim to fulfill the requirements of Article 83 EPC the patent has to disclose the suitability of the product to be manufactured for the claimed therapeutic application.

22. A claimed therapeutic application may be proven by any kind of evidence as long as it reflects the therapeutic effect on which the therapeutic application relies (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, section II.C.6.2; in

particular decisions T 609/02, point 9 of the reasons, and T 801/06, point 28 of the reasons, both cited in that section). Evidence reflecting a therapeutic effect is sometimes also referred to as evidence that makes the therapeutic effect "plausible" or "credible".

23. In the present case, the therapeutic application is "treating or preventing pain syndromes with a substantially peripheral or central neurogenic component". Hence, the therapeutic effect to be achieved by the compounds referred to in the claims can be seen as the reduction or prevention of pain. The question to be addressed is thus whether or not the evidence provided in the patent reflects this therapeutic effect.

24. The patent discloses that enovin was found to induce neurite extension in SH-SY5Y human neuroblastoma cells (see paragraph [0088] and Figure 7). It was also observed that taxol induced neuronal apoptosis in NGF-differentiated PC12 rat pheochromocytoma cells (see paragraph [0089]). Thus, it was concluded that taxol-induced cytotoxicity has features of neuronal apoptosis and it could be deduced that, if it were applied, taxol would induce apoptosis in differentiated SH-SY5Y cells (*ibid.*). Moreover, enovin was shown to protect differentiated SH-SY5Y against taxol-induced cell toxicity (see paragraph [0091] and Figure 6).

25. Based on the effect of enovin on the survival of different neuronal cell populations and on the observed neurite extension in SH-SY5Y cells, the patent went on to investigate whether enovin possessed neuroregenerative properties. To this end pilot trials were conducted to test whether enovin was able to change the taxol-induced sensory deficits in rats after

subplantar injections in rats using the pin prick test.

26. In a first experiment (see paragraphs [0103] to [0107], Figure 19), it was tested whether a single treatment with enovin could reverse the taxol-induced sensory deficit. Repeated subplantar injections of taxol over three consecutive days were found to result in an acute inflammatory reaction with a lack of response to pin prick stimulation in the majority of the animals. Upon a single subplantar injection of enovin, at day 8, all 10 animals responded at least once to the pin prick, and a normal reactivity was present in 5 out of 10 rats. Thus, it was concluded that enovin could restore the taxol-induced sensory deficit.

27. In a second experiment (see paragraphs [0108] to [0112], Figure 20), it was tested whether enovin could prevent the development of taxol-induced deficits. Pretreatment with enovin reduced the taxol-induced deficits on the pin prick. At day 1, 8 out of 10 animals responded at least once to pin prick stimulation.

28. The experimental models used in the patent are based on the premise that taxol causes nerve damage and that nerve damage causes pain. The board notes that at the effective date of the patent it was indeed known that taxol, an established cytotoxic anti-cancer drug, had well known side-effects, including peripheral neuropathy. Document D39 provides evidence that neuropathy occurs as one of the toxic side-effects of taxol treatment and that nerve damage can manifest itself as pain.

29. The regained sensation in the experiments described above (see points 26 and 27) can therefore be taken as

an indication of the regeneration of the nerve cells. Therefore it can be concluded that enovin rescues the nerve damage caused by taxol by regenerating the damaged nerves and thus that enovin has the potential to be effective in ameliorating the side-effects of taxol, e.g. neuropathic pain. Accordingly, the taxol-based models in the patent, both *in vitro* and *in vivo*, reflect the therapeutic effect on which the claimed treatment with enovin relies.

30. The appellants questioned the evidential value of the rat models used in the patent, since the treatment of pain was not directly shown.

31. However, in accordance with the relevant case law (see point 22 above), the therapeutic effect does not have to be directly shown in order for the suitability of a compound for a treatment to be acknowledged. It is sufficient that there is evidence that reflects the therapeutic effect or makes it "plausible" or "credible". In the light of (i) the link between taxol-induced neuropathy and pain known in the art (see point 28 above), (ii) the *in vitro* effect of enovin on taxol-treated nerve cells shown in the patent (see point 24 above), (iii) the specificity of enovin for nerve cells shown in the patent (*ibid.*) and (iv) the reversal of taxol-induced sensory dysfunction shown in the patent (see point 26 above), the board is satisfied that the animal models render it plausible that enovin rescues damaged nerve cells and hence is suitable for the treatment of pain arising from the nervous system itself.

32. Finally, the appellants submitted that the skilled person would be at a loss when trying to establish whether he was working in the area of the claims

because the term "with a substantially peripheral or central neurogenic component" had no recognised meaning in the art. Pursuant to decision T 464/05, point 3.3.5 of the reasons, this would result in a lack of sufficiency of disclosure.

33. Article 83 EPC stipulates that the European patent application "shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art". It has been established above (see points 21 to 31) that the invention can be carried out by the person skilled in the art.

34. The board considers the question of whether or not the skilled person knows if he is working within or outside the area of the claims to be a question of knowing what is the subject-matter for which protection is sought and thus to be a matter for Article 84 EPC (clarity) and not Article 83 EPC (sufficiency of disclosure).

35. Decision T 464/05 relied on by the appellants relates to a case in which a parameter, mass vapour transmission rate (MVTR), was referred to in the claims, while the patent did not describe in detail a test method for measuring the MVTR. Since the appellants' argument does not concern the measurement of parameters, but rather the clarity of an expression, decision T 464/05 is not considered to be pertinent. Moreover, the board considers that the term in dispute is clear (see point 20 above).

36. For the reasons indicated above the board decides that the main request complies with the requirements of Article 83 EPC.

Novelty (Article 54(3) EPC)

37. It was common ground between the parties that the effective date for assessing the novelty of the subject-matter of claims 14, 16, 17 and 19 is the third priority date.

38. Claims 14, 16, 17 and 19 are drafted as second medical use claims (see section X above for the complete wording of the claims). Pursuant to established case law, a disclosure destroys novelty only, if the teaching it contains is reproducible or "enabling" (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, section I.C.3.11, and in particular decision T 1437/07, reasons, points 25 and 26, cited in that section). For the requirement of reproducibility to be considered fulfilled in relation to a medical use it is necessary for the patent to disclose the suitability of the product to be manufactured for the claimed therapeutic application (see point 21 above).

39. Thus, in the present case, a prior art document would be novelty-destroying only if it not only disclosed the product referred to in the claim (in this case for example a nucleic acid molecule encoding a sequence which has at least 70% amino acid homology with the amino acid sequence of SEQ ID NO:4) for the claimed therapeutic application (in this case treating or preventing pain syndromes with a substantially peripheral or central neurogenic component), but also disclosed that the product referred to in the claim was indeed suitable for the claimed therapeutic application.

40. Documents D4 and D6 are the only documents cited by the appellants in the appeal proceedings under Article 54 EPC, more particularly under Article 54(3) EPC. It is undisputed that only the disclosure of document D4, as far as it is entitled to the claimed priority of document D5, and only the disclosure of document D6, as far as it is entitled to the priority of document D9, can be considered relevant prior art under Article 54(3) EPC for the claimed subject-matter.

41. In the present circumstances, for documents D4 or D6 to anticipate the subject-matter of e.g. claim 14, the suitability of a nucleic acid molecule encoding a sequence which has at least 70% amino acid homology with the amino acid sequence of SEQ ID NO:4 for the therapeutic application must thus be disclosed in both the respective priority documents D5 and D9, and in documents D4 and D6, respectively. This follows from Article 89 EPC in combination with G 2/98 (OJ EPO 2001, 413, reasons, point 9), where the Enlarged Board endorsed a narrow or strict interpretation of the concept of "the same invention", limiting the right to priority to subject-matter which the person skilled in the art can derive directly and unambiguously, using common general knowledge, from the previous application as a whole (see also decision T 107/09, reasons, points 7 to 10).

42. Document D5 relates to the cloning and characterisation of a neurotrophic factor termed GRNF4 and mentions that it might be used in treatment *inter alia* of peripheral sensory neuropathy (see page 7, lines 14 to 16). The most relevant examples, examples 10 and 11 (see page 74, line 30, to page 75, line 26), show the ability of GRNF4 to induce autophosphorylation of the orphan Ret receptor protein tyrosine kinase. Document D5 thus

shows the binding of GRNF4 to its receptor, but no effect of GRNF4 on nerve cells, and in particular no data that would allow it to be concluded that GRNF4 induces the regeneration of nerve cells. The board considers that the data provided by document D5 is not suited to make the treatment of peripheral sensory neuropathy with GRNF4 at least plausible.

43. Document D9 relates to the cloning and characterisation of a neurotrophic factor termed artemin (see page 6, lines 2 to 19) and mentions (see page 9, lines 2 to 4) that it is useful for the treatment *inter alia* of peripheral neuropathy. The document provides data showing that artemin promotes the survival of peripheral and central neurons in culture (examples 4 and 6) and that artemin signals through RET (examples 5 and 7), but is silent on the regeneration of nerve cells. The board considers that this data does not make it at least plausible that artemin can be used to treat peripheral neuropathy.

44. The appellants submitted that both document D5 and document D9 disclosed that GNRF4 and artemin, respectively, were suited for treating conditions falling under the term "pain syndromes with a substantially peripheral or central neurogenic component". Their objection rested on the premise that if nerve damage was treated, its side-effect - pain - was necessarily treated, too. However, this argument fails because the treatment of nerve damage is not credibly disclosed in either document D5 or document D9 (see points 42 and 43 above).

45. Thus, neither document D5 nor document D9 can be regarded as disclosing the suitability of GRNF4 or artemin, respectively, for "treating or preventing pain

syndromes with a substantially peripheral or central neurogenic component".

46. Hence, document D4 is not entitled to the priority of document D5, and document D6 is not entitled to the priority of document D9. Document D4 and document D6 cannot therefore be considered prior art under Article 54(3) EPC for the claimed subject-matter, and consequently they do not anticipate the subject-matter of claims 14, 16, 17 and 19.

47. Therefore the board is satisfied that the subject-matter of claims 14, 16, 17 and 19 is novel within the meaning of Article 54(3) EPC over the disclosure of document D4 and document D6.

Inventive step (Article 56 EPC)

Closest prior art

48. For the assessment of inventive step the Boards of Appeal apply the "problem and solution approach" which, as a first step, requires the "closest prior art" to be defined. In accordance with the established case law of the Boards of Appeal the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, I.D.3.1).

49. In the present case, the invention aims at the treatment of pain syndromes with a substantially

peripheral or central neurogenic component. The opposition division and the appellants considered that document D2 represented the closest prior art.

50. Document D2 reports the identification of artemin, a novel member of the glial cell line-derived neurotrophic factor (GDNF) family. The mature artemin protein of document D2 is 100% identical to the part of the sequence of SEQ ID NO:4 that corresponds to mature "enovin". This document discloses that neurotrophic factors are known to orchestrate multiple aspects of the development and maintenance of the central and peripheral nervous system and that all known members of the GDNF family of ligands have neurotrophic properties and support the survival of dopaminergic midbrain neurons and spinal and facial motor neurons in both *in vitro* survival and *in vivo* injury paradigms. Document D2 moreover shows that artemin is a survival factor for sensory and sympathetic neurons in culture and that it is up-regulated after nerve injury.

51. Document D2 is however silent about any therapeutic use of artemin in general or the treatment of neurogenic pain in particular. Thus, although document D2 discloses a compound which is structurally close to the compounds referred to in the claims at issue, it fails to disclose subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention. Accordingly, document D2 does not qualify as the closest prior art document.

52. In contrast, document D38 relates to the diagnosis and treatment of neurogenic pain and discloses a variety of drugs that are used in the pharmacotherapy of neurogenic pain (see Table 2). According to document D38, antidepressants provide analgesia in a subgroup of

patients with peripheral and central neurogenic pain states (see paragraph bridging pages 4 and 5). Finally, document D38 discloses that the available drugs offer substantial pain relief to no more than half of those afflicted with neurogenic pain and that therefore new drugs are needed (see page 7, lines 1 to 3). Document D38 thus discloses subject-matter conceived for the same purpose as the claimed invention and therefore qualifies as the closest prior art document.

53. It follows that the appellants' arguments, which are all based on the premise that document D2 is the closest prior art document (see section XI, above), fail for this reason alone.

Technical problem to be solved and its solution

54. Starting from document D38 the technical problem to be solved consists in the provision of alternative means for the therapy of peripheral or central neurogenic pain states.

55. As the solution to this problem, claim 14 proposes the use of a nucleic acid molecule encoding a sequence which has at least 70% amino acid homology with the amino acid sequence of SEQ ID NO:4.

56. The claim under consideration is drawn up in the so-called Swiss-format, and the statement of purpose thus limits the claim to molecules that are useful for the purpose of preparing a medicament for treating or preventing pain syndromes with a substantially peripheral or central neurogenic component (cf. decision T 1031/06, point 23 of the reasons). In view of the finding with respect to sufficiency of disclosure (*supra*, see points 21 to 36 of the reasons),

the board is satisfied that there is evidence in the patent to the effect that the whole subject-matter as claimed is to be regarded as a solution to this problem.

Obviousness

57. The question to be answered is whether the skilled person, when facing the technical problem defined above, i.e. the provision of alternative means for the therapy of peripheral or central neurogenic pain states, would have modified the teaching in the closest prior art document D38 so as to arrive at the claimed invention in an obvious manner.

58. Document D38 discloses that the drugs for treating neurogenic pain include antidepressants, anticonvulsants, antiarrhythmics, local anaesthetics and opioids (see Table 2). Observations from clinical studies, clinical anecdotes and experimental findings led to the identification of these drugs (see page 4, second paragraph). Finally document D38 discloses that knowledge of pathophysiologic mechanisms underlying neurogenic pain has grown exponentially during the last decade and offers many possible approaches for pharmaceutical intervention, such as the use of neurotransmitter antagonists given singly or with other drugs to decrease excitability at the membrane level or inhibit different steps of the nociceptive transmission process.

59. Document D38 is however silent about the possible use of neurotrophic factors in general or of enovin or enovin-like compounds in particular (see point 2 above for the different terms used in the art for enovin) in the treatment of peripheral or central neurogenic pain

states. The board concludes that document D38 on its own provides no hint at the subject-matter of claim 14 as a solution to the underlying problem.

60. As set out above, document D2 discloses that artemin, which has the same amino acid sequence as enovin (see point 50 above), is a survival factor for sensory and sympathetic neurons in culture and that it is up-regulated after nerve injury. Document D2 makes no reference to the treatment of neurogenic pain. Document D2 therefore provides no motivation for using artemin, and thus enovin, to solve the problem formulated above.

61. Documents D33 to D35 disclose GDNF, which is like artemin/enovin, a member of the GDNF family of proteins, and identify it as a possible target in the treatment of peripheral neuropathies or in the development of novel analgesic therapies. However, although both artemin/enovin and GDNF are members of the GDNF family of molecules, they are structurally very divergent (see document D2, paragraph bridging pages 1292 and 1293). In fact, artemin/enovin is structurally most similar to neurturin (NTN) and persephin (PSP). Moreover, artemin/enovin is unique amongst the members of the GDNF family in that it signals through the orphan receptor GFRα3.

62. Given these structural and functional differences between artemin/enovin and GDNF, the board is not persuaded that, on the basis of any of documents D33 to D35, the person skilled in the art would have had any expectations with regard to the therapeutic properties of artemin/enovin at all, let alone that it would be useful in the treatment of peripheral or central neurogenic pain states. Indeed, a factor that is known to promote the survival and maintenance of neurons is

not necessarily useful for treating neuropathic pain, and it could not have been ruled out that artemin, like NGF, would induce pain (see document D34, page 3070, right hand column, third paragraph).

63. In summary, the board concludes that none of the documents relied on by the appellants provides any hint that would have motivated the skilled person to modify the teaching in the closest prior art document D38 so as to arrive at the claimed invention in an obvious manner.

64. The above considerations in respect of claim 14 of the main request apply *mutatis mutandis* to the subject-matter of independent claims 16, 17 and 19. The main request fulfils the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of the main request filed during the oral proceedings on 13 November 2014 and a description and figures to be adapted thereto.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated