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**Datasheet for the decision
of 1 December 2016**

Case Number: T 2055/12 - 3.3.04

Application Number: 06075704.4

Publication Number: 1690547

IPC: A61K39/00, A61K39/39, A61P25/28

Language of the proceedings: EN

Title of invention:
Prevention and treatment of amyloidogenic disease

Patent Proprietor:
Janssen Alzheimer Immunotherapy

Opponents:
H. Lundbeck A/S
Esslinger, Dr., Alexander (opposition withdrawn)
AC Immune S.A.
Meier, Jürgen

Headword:
Amyloidogenic disease/JANSSEN

Relevant legal provisions:
EPC Art. 83, 100(b)
EPC R. 115(2)
RPBA Art. 15(3)

Keyword:

"sufficiency of disclosure - all claim requests (no)"

Decisions cited:

T 0609/92, T 0063/06

Catchword:

-



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Case Number: T 2055/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 1 December 2016

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
28 June 2012 concerning maintenance of the
European Patent No. 1690547 in amended form.**

Composition of the Board:

Chairwoman G. Alt
Members: B. Claes
M. Blasi

Summary of Facts and Submissions

- I. Appeals were lodged by the patent proprietor (hereinafter "appellant I") and opponents 01 to 03 (hereinafter "appellants II to IV") against the interlocutory decision of the the opposition division concerning maintenance of the European patent No. 1 690 547 in amended form. The patent is based on European patent application 06075704.4 which was filed as a divisional application of the earlier European patent application No. 98961833.5 and has the title "*Prevention and treatment of amyloidogenic disease*". Opponent 04 (hereinafter "respondent") did not file an appeal and is a party to these appeal proceedings as of right (Article 107 EPC).

Claim 1 of the patent as granted read:

"1. A pharmaceutical composition for use in treatment or prevention of disease comprising an immunogenic agent effective to induce an immunogenic response against A β in a patient, and a pharmaceutically acceptable adjuvant, wherein the agent is A β or an immunogenic fragment of A β ."

- II. The patent was opposed based on the grounds for opposition in Article 100(a) EPC (novelty and inventive step) and in Articles 100(b) and (c) EPC.
- III. In the decision under appeal the opposition division held that some of the claims of the main request related to added subject-matter. Concerning the claims of auxiliary request 1 it was found that that the requirements of Articles 76(1) and 123(2) EPC, of Article 83 EPC and Article 54(1), (2) EPC were met, but that the subject-matter of the claims lacked an

inventive step (Article 56 EPC). The patent in the form of auxiliary request 2 met the requirements of the EPC.

IV. With its statement of grounds of appeal appellant I re-submitted the main request and auxiliary requests 1 and 2 pending before the opposition division. With the reply to the appeals of the opponents it further submitted auxiliary requests 3 and 4.

Claim 1 of the **main request** and of **auxiliary request 1** was identical to claim 1 as granted (see section I).

Claim 1 of **auxiliary request 2** read:

"1. A pharmaceutical composition for use in treatment or prevention of disease comprising an immunogenic agent effective to induce and that induces an immunogenic response against A β in a patient, and a pharmaceutically acceptable adjuvant that enhances the response, wherein the agent is A β or an immunogenic fragment of A β ." (emphasis added by the board)

Claim 1 of **auxiliary request 3** read:

"1. A pharmaceutical composition for use in treatment or prevention of Alzheimer's disease comprising an immunogenic agent effective to induce an immunogenic response against A β in a patient, and a pharmaceutically acceptable adjuvant, wherein the agent is A β or an immunogenic fragment of A β ." (emphasis added by the board)

Claim 1 of **auxiliary request 4** read:

"1. A pharmaceutical composition for use in treatment or prevention of disease comprising an immunogenic

agent effective to induce an immunogenic response against A β in a patient, and a pharmaceutically acceptable adjuvant, wherein the agent is an immunogenic fragment of A β from the N-terminal half of A β ." (emphasis added by the board)

- V. In the appeal proceedings the written submissions of appellants II to IV focused *inter alia* on the fact that the claimed invention as subject-matter of the main request and of auxiliary requests 1 and 2 was not disclosed in a manner sufficiently clear and complete for it to be carried out by the skilled person (Article 83 EPC).
- VI. Appellant III (opponent 02) withdrew its appeal and opposition.
- VII. The board summoned the parties to oral proceedings. Appellants I and IV and the respondent announced that they would not be attending.
- VIII. Oral proceedings before the board were held on 1 December 2016. The duly summoned appellants I and IV and the respondent were not present as announced. At the end of the oral proceedings the chairwoman announced the board's decision.
- IX. The following documents are referred to in this decision:
- D56: Zotova *et al.* (2010), *Alzheimer's Research and Therapy*, Vol. 2, No. 1. pages 1-9.
- D81: Wilcock *et al.* (2004), *J. Neurosci.*, Vol 24, No. 27, pages 6144-6151.

D82: Deane *et al.* (2005), *J. Neurosci.*, Vol 25,
No. 50, pages 11495-11503.

- X. The arguments of appellant I in relation to sufficiency of disclosure and relevant for this decision can be summarised as follows:

The patent demonstrated that A β or an immunogenic fragment of A β administered with an adjuvant was capable of raising an immune response. This was the first disclosure of immunotherapy of an amyloidogenic disease, such as Alzheimer's disease. The invention thus opened up a whole new field and was entitled to more generality in the claims than one which was concerned with advances in a known technology.

In view of the data in the patent there existed a strong presumption that the patent related to an invention which was disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (see decision T 63/06).

The in-depth experimental analysis in the patent in suit showed that A β 1-5, A β 1-12, A β 13-28 and A β 1-42 were able to reduce the hallmark pathologies of Alzheimer's disease and these results were corroborated in a number of post-published publications. The data in the examples comprehensively described that a reduction in amyloid burden was achieved across the scope of the claims. The immune responses mediated the beneficial response, *i.e.* therapeutic efficacy. The results achieved by using A β 1-42 were also achieved by using a fragment thereof.

Although A β clearance following administration did not reach statistical significance, it was clear from

Figure 12 of the patent that reductions in amyloid burden were also seen for the tested A β 1-12 conjugate and A β 13-28 conjugate. Thus Figure 12 showed that multiple different fragment conjugates within the scope of the claims reduced amyloid burden, with the A β 1-5 conjugate reaching a statistically significant level.

Document D56 comprised a summary of useful fragments falling within the scope of the claims (page 6, first column, final paragraph) and noted the clinical studies relying on active immunisation with A β 1-6, as well as on passive immunisation with antibodies against A β 33-40, A β 13-28 and A β 1-5 and with intravenous immunoglobulin. Documents D81 and D82 confirmed that peptides covering epitopes from within the mid-region and the C-terminus of A β provided a beneficial therapeutic effect by active immunisation in transgenic mice models.

XI. Appellants II and IV's arguments in relation to sufficiency of disclosure and relevant for this decision can be summarised as follows:

The patent did not demonstrate the medical and therapeutic utility of the compositions (fragments) over the whole scope of the claims.

Example IV was the only example that related to conjugates of fragments of A β , namely A β 1-5, A β 1-12, A β 13-28 and A β 33-42. The conjugated fragment A β 1-5-IgG as adjuvanted with CFA was the only conjugated fragment providing significant cortical A β and plaque reduction (see paragraphs [0127], [0128], [0131] and [0132] of the patent).

A β 1-12 gave neither rise to significant cortical A β reduction nor to significant cortical plaque reduction, although a high peak antibody response was detected for A β 1-12. In fact, a comparison of the results of Figures 12 and 13 of the patent in suit clearly demonstrated that the efficiency of inducing an immune response did not stand in a direct correlation with the efficacy of reducing amyloid plaques in the brain. Thus, although immunisation with some A β peptides lead to the production of antibody titers, not all A β -specific antibodies were able to reduce amyloid plaque burden in the brain.

Due to the lack of correlation between A β -specific antibody titers and plaque reduction in the brain, the former was thus not a guide to efficacy and made therefore the choice of the right peptide antigen totally unpredictable, as even the patent acknowledged (see paragraphs [0135] and [0143]). Consequently, it was undue burden for the skilled person to practice the invention over the whole scope of the claim as the skilled person, following the teaching of the patent, was not sure that by using a conjugate of a preferred fragment coupled to a preferred carrier a detectable antibody response would be achieved, let alone plaque reduction in the brain.

XII. Appellant I requested in writing that the decision under appeal be set aside and the patent be maintained on the basis of the claims of the main request, or alternatively, of auxiliary request 1 both as filed with its statement of grounds of appeal, or alternatively, that the other appellants' appeal be dismissed, or further alternatively, that the decision under appeal be set aside and the patent be maintained on the basis of one of the sets of claims of auxiliary

requests 3 or 4 as filed with its letter dated 26 March 2013.

Appellant II and, in writing, appellant IV requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

1. In the course of the appeal proceedings, appellant III withdrew its opposition and appeal. In view of this withdrawal appellant III ceased to be a party to the appeal proceedings as regards substantive issues. Other issues for which it would have remained a party to the proceedings did not arise in the present case. Appellants I, II and IV's appeals against the interlocutory decision are not affected by this withdrawal.
2. Appellants I and IV and opponent 04 were duly summoned to the oral proceedings before the board, but did not attend. In accordance with Rule 115(2) EPC and Article 15(3) RPBA the proceedings were continued in their absence. These parties were treated as relying on their written cases.

Introduction to the invention

3. Alzheimer's disease (AD) is characterised by the presence of amyloid deposits, also known as senile plaques, in the brain of AD patients. The β -amyloid peptide or A β peptide is the principal constituent of these amyloid deposits and is a natural proteolytic fragment of 39 to 43 amino acids in length of the amyloid precursor protein (APP). Several mutations within APP have been correlated with the presence of AD

and are thought to increase the amount of pathogenic A β , in particular the long forms having a length of 42 or 43 amino acids. These long forms of A β are therefore thought to constitute a causative element in AD (see e.g. paragraph [0003] of the patent in suit).

4. The present invention concerns active immunisation in the "*treatment or prevention of disease*" such as AD based on the administration of the A β peptide or an immunogenic fragment thereof "*to induce an immunogenic response to A β in a patient*".

Sufficiency of disclosure (Article 83 and 100(b) EPC)

Main request and auxiliary request 1 - claim 1

5. The opposition division held in the decision under appeal that "*there is no evidence on file to support the Opponents [sic] contention that the skilled artisan is unable to find suitable fragments [...] using conventional methods or that this burden is unreasonable*" (see point 28.2 of the Reasons). With their appeals the opponents *inter alia* have maintained their objection that the invention as subject-matter of the claims was not disclosed in a manner sufficiently clear and complete for it to be carried out by the skilled person (Article 100(b) EPC).
6. It is established case law of the boards of appeal (see Case Law of the Boards of Appeal of the EPO, 8th Edition 2016, hereinafter "CLBA", II.C.6.2) that when assessing claims pertaining to a therapeutic effect such as purpose-limited product claims in accordance with Article 54(4) and 54(5) EPC or claims drafted in accordance with the "Swiss-type format", attaining the claimed therapeutic effect is a functional technical

feature of the claims (see e.g. decision T 609/92 of 27 October 2004). As a consequence under Article 100(b) EPC, unless this is already known to the skilled person at the priority date, the patent in suit must disclose the suitability of the product to be manufactured for the claimed therapeutic application. Clinical trials are not required to establish suitability. It may suffice that *in vitro* or *in vivo* data directly and unambiguously reflect the therapeutic effect on which the claimed therapeutic application relies or, alternatively, establish a relationship between the physiologic activities of the compound under consideration and the claimed disease.

7. In the present case the subject-matter of claim 1 (see sections I and IV) is for a pharmaceutical composition for use in treatment or prevention of disease comprising an agent which is effective to induce an immunogenic response against A β in a patient, wherein the agent is either (i) A β or (ii) an immunogenic fragment thereof.
8. It is uncontested that the prior art does not disclose experimental evidence that administration of A β or immunogenic fragments thereof attain a therapeutic effect in the treatment or prevention of a disease such as AD. Accordingly, the question to be assessed in the context of Article 100(b) EPC in the present case is whether or not the patent provides information such as evidence, which, having due regard of the common general knowledge, would demonstrate the suitability of the embodiments of claim 1 for the claimed therapeutic application.
9. Several examples in the patent disclose the immunisation of so-called PDAPP mice with either long

versions of A β or conjugated and non-conjugated fragments thereof.

- 9.1 PDAPP mice (see paragraph [0080] of the patent) are transgenic for the human APP gene, having a point mutation at a particular position of the protein sequence (see point 2 above). Expression of this gene inevitably causes onset of the formation of A β amyloid deposits or plaques in mouse brains at an age of six months. By fifteen months of age these mice exhibit levels of A β deposition equivalent to that seen in AD. Accordingly, the PDAPP mice are an animal model for evaluating the effectiveness of therapeutic agents in the treatment of human AD.
- 9.2 Examples I and II disclose that the immunisation of PDAPP mice with human aggregated A β 1-42 ("A β 1-42" referring to the 42 amino acids long form of A β) results in a dose-dependent formation of anti-A β antibodies and the prevention of A β plaque formation, while non-immunised control mice develop plaques.
- 9.3 Example III of the patent in suit shows that the immunisation of PDAPP mice with human aggregated A β 1-42 reduces amyloid plaque deposits already established in the brain (see paragraph [0107]; Figure 7 and table 2 for the cortical A β and A β 1-42 amyloid burden and table 3 for the hippocampus A β and A β 1-42 amyloid burden). An analysis of the brains after immunisation further indicates that activated phagocytic microglia and monocytes, i.e. cell-mediated processes, are involved in plaque removal (see paragraphs [0110] and [0114]).
- 9.4 Example IV concerns the screening of fragments in nine different regions of APP and A β in the immunisation of PDAPP mice to determine which epitopes convey the

response reported on in example III (see paragraph [0126]). The immunogens include four specific human A β fragment conjugates. Example IV reports that a reduction of established amyloid plaques, including a reduction in total A β in the brain of PDAPP mice, is achieved by immunisation with a conjugated A β 1-5 fragment, *i.e.* a fragment being derived from the N-terminus of human A β and linked to sheep anti-mouse IgG (see [0135] and the summary in paragraph [0139]). It is further reported that the immunisation of PDAPP mice with conjugates of the three other human A β fragments which were screened, *i.e.* sheep anti-mouse IgG-conjugated A β 1-12, A β 13-28 and A β 33-42 fragments as well as an aggregated A β 25-35 fragment (see paragraphs [0126] and [0131]) do not significantly reduce either the amount of established amyloid plaques or the total amount of A β in the brain of PDAPP mice (see paragraphs [0139] and [0140] and figures 11 and 12).

10. The board notes that the patent, in example IV, accordingly demonstrates a lack of therapeutic effect for the specific A β fragment conjugates and aggregates originating from the central and C-terminal region. It appears that this lack of therapeutic effect is not due to the absence of generated anti-A β antibodies because in the serum and on cerebral A β plaques polyclonal antibodies binding to A β are detectable (see paragraph [0142]). Also the level of anti-A β antibody titer induced by the conjugated fragments appears not to correlate with the lack of therapeutic efficacy, since those fragment conjugates which elicit a high antibody titer fail to achieve a significant therapeutic effect (*i.e.* A β 1-12), while others which elicit a low titer are either effective (A β 1-5) or not (A β 13-28 and A β 33-42) (see paragraph [0143]).

11. In the context of example IV appellant I has argued that although A β clearance following administration of certain A β conjugates did not reach statistical significance, it was however clear from Figure 12 of the patent in suit that reductions in amyloid burden were also seen for the A β 1-12 and A β 13-28 conjugate. Figure 12 thus demonstrated that multiple different fragment conjugates within the scope of the claims reduced the amyloid burden, with the A β 1-5 conjugate however reaching a statistically significant level.

12. The board notes in this context that it is the patent itself which distinguishes in paragraphs [0139] and [0140] of the description, when contemplating the results of the experiments, a reduction of amyloid burden which is statistically significant and which is not. In the board's opinion this reflects an important component of proper scientific methodology to base conclusions on correlation of effects on statistical significance rather than on subjective observation. Accordingly, the board judges that, independently of whether or not the contention of appellant I is correct in relation to Figure 12, results which are statistically non-significant fail to demonstrate a particular correlation. Consequently, appellant I's subjective interpretation of the results in experiment IV does not convince the board.

13. Accordingly, it can be derived from examples III and IV of the patent that the therapeutic effect which can be observed upon immunisation of PDAPP mice with human aggregated A β 1-42 can be accepted to be mirrored in the therapeutic effect attained by the immunisation with the N-terminal and sheep anti-mouse IgG-conjugated A β 1-5 fragment. However, all other sheep anti-mouse IgG-conjugated human A β fragments tested, including

also the conjugated A β 1-12 fragment, which contains as such the A β 1-5 fragment, failed to demonstrate suitability for the claimed therapeutic application.

14. The board is satisfied that it can be concluded from these results that the A β 1-5 fragment obviously comprises an epitope which elicits an effective and presumably a cell-based immune response against A β in amyloid plaques, while a conjugate comprising an A β 1-12 fragment obviously lacks this epitope since no effective immune response is induced. A similar conclusion may be drawn for the conjugates comprising either A β 13-28 or A β 33-42 which are derived from the central or C-terminal region of human A β respectively.
15. It is established case law of the Boards of Appeal (CLBA, II.C.5.6.1) that, even though a reasonable amount of trial and error is permissible when it comes to sufficiency of disclosure, e.g. in an unexplored field or where there are many technical difficulties, the skilled person has 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 through the evaluation of initial failures. Where the skilled person can only establish by trial and error whether or not his particular choice of numerous parameters will provide a satisfactory result, this amounts to an undue burden.
16. It follows from the observations in point 9 above that in the present case the patent - there is no other more instructive disclosure than the examples - fails to provide the skilled person a rationale, without trying each and every fragment individually, for determining whether or not a defined fragment is suitable to elicit the beneficial immune response which leads to the

envisaged and claimed therapeutic effect since neither the location of the fragment within full-length A β nor its immunogenicity appears to indicate the suitability for the therapeutic application. The board notes that the above conclusion appears to even more apply to fragments of human A β defined in claim 1 which are not conjugated at all or are conjugated to proteins other than sheep anti-mouse IgG.

17. The board considers therefore that, in the present circumstances, the skilled person is in a trial and error situation and that carrying out the invention across its whole ambit amounts to an undue burden.
18. Appellant I submitted that according to e.g. decision T 63/06 of 24 June 2008 (see point 3.3 of the reasons) in view of the detailed disclosure of the invention supported by abundant experimental evidence in the patent in suit a strong presumption existed that the patent as granted sufficiently disclosed the claimed invention and that the opponents bore the burden of proof for establishing insufficiency of disclosure.
19. While in general the board agrees with the appellant regarding the principles established in decision T 63/06, *supra*, it is noted that the situation in the present case is different from that underlying this decision, since, as outlined above, the patent in suit itself already discloses experimental evidence that certain fragments from different regions of A β are unsuitable for the claimed therapeutic application. The board considers that, under these circumstances, it is not necessary for the opposing parties to provide even further evidence as they can rely on the evidence provided by the patent itself.

20. Appellant I has further submitted that also post-published disclosures documented the suitability of various fragments across the scope of the claims for the therapeutic application. In particular document D56 comprised a summary of useful fragments which fell within the definition on claim 1 (page 6, first column, final paragraph) and noted the clinical studies relying on active immunisation with A β 1-6, as well as on passive immunisation with antibodies against A β 33-40, A β 13-28 and A β 1-5 and with intravenous immunoglobulin. Similarly, documents D81 and D82 confirmed that epitopes within the mid-region and the C-terminus of A β provided a beneficial therapeutic effect in transgenic mice models.
21. The board notes that, like the disclosures in documents D81 and D82, the relevant experiments referred to in document D56, except one, concern passive immunisation with antibodies recognising certain epitopes on A β . Furthermore, document D56 appears to concern ongoing clinical trials without reporting results. Since the claimed invention is for active immunisation with fragments of A β , however, possible results of such experiments cannot appropriately be considered for remedying failure to demonstrate suitability of agents in the patent for the therapeutic application.
22. The board notes in this context that a consequence of the above finding is furthermore that, under the circumstances of the present case, the reasons why the board has admitted documents D56 to D86 into the proceedings, does not need to be further elaborated on.

23. In view of the above considerations the board judges that the patent fails to disclose the invention as defined in claim 1 of the main request and auxiliary request 1 in a manner sufficiently clear and complete for it to be carried out by the the skilled person (Article 100(b) EPC).

Auxiliary requests 2 to 4 - claim 1

24. The subject-matter of claim 1 of auxiliary request 2 differs from claim 1 of the main request in that it is specified that the immunogenic agent is not only *"effective to induce"*, but now also *"induces an immunogenic response against A β in a patient"* and that the adjuvant is one *"that enhances the response"*. In claim 1 of auxiliary request 3 it is specified that the disease is Alzheimer's disease.
25. The board's finding that the patent lacks sufficiency of disclosure in the context of the invention as defined in claim 1 of main request and auxiliary request 1 is not based on the fact that fragments of A β fail to induce an immunogenic response, but rather on the failure of demonstration suitability for the claimed therapeutic effect in relation to disease, be it AD or similar, despite inducing an immunogenic response against A β . Accordingly, the specifications provided by the amendments in claims 1 of auxiliary requests 2 and 3 cannot remedy the attested insufficiency.
26. Claim 1 of auxiliary request 4 specifies that the immunogenic fragment of A β is from the N-terminal half of A β . In this context the board refers to the results in Example IV showing that, in contrast to the situation with a A β 1-5 conjugate, no therapeutic effect

could be demonstrated for a conjugate of A β 1-12, whereby both fragments are situated in the N-terminus of A β (see point 10 above). The amendment amounting to the specification that the fragments are derived from the N-terminal half of A β can therefore also not remedy the attested finding of lack of sufficiency of disclosure.

27. In view of the above considerations, the reasons and conclusion set out in the context of claim 1 of the main request and auxiliary request 1 apply *mutatis mutandis* to the patent in suit in the form of auxiliary requests 2 to 4 (Article 83 EPC).

Order

For these reasons it is decided that:

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

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated