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**Datasheet for the decision
of 22 May 2012**

Case Number: T 1309/08 - 3.3.04

Application Number: 01900978.6

Publication Number: 1246638

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Language of the proceedings: EN

Title of invention:
Use of exendins and agonists thereof for the treatment of
hypertriglyceridemia

Applicant:
AMYLIN PHARMACEUTICALS, INC.

Opponents:
Novo Nordisk A/S
Sanofi-Aventis Deutschland GmbH

Headword:
Exendins/AMYLIN PHARMACEUTICALS, INC.

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2)

Keyword:
"Main request and auxiliary requests 1 to 3: added subject-
matter (yes)"
"Auxiliary request 4: added subject-matter (no), sufficiency
of disclosure (yes), novelty (yes), inventive step (yes)"

Decisions cited:

T 0497/02, T 1321/04

Catchword:

-



Case Number: T 1309/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 22 May 2012

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted 6 May 2008
revoking European patent No. 1246638 pursuant
to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: R. Gramaglia
R. Morawetz

Summary of Facts and Submissions

I. European patent No. EP-B-1 246 638 (application No. 01 900 978.6) having the title "Use of exendins and agonists thereof for the treatment of hypertriglyceridemia" was granted with 21 claims.

II. Notices of opposition were filed by opponents OI and OII requesting the revocation of the European patent in view of Articles 100 (a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step (Articles 54 and 56 EPC), had not been sufficiently disclosed (Article 83 EPC) and extended beyond the content of the application as originally filed (Article 123(2) EPC).

III. The opposition division came to the conclusion that the claims then on file did not comply with the requirements of the EPC and revoked the patent.

IV. The appellant (patentee) filed an appeal against the decision of the opposition division.

V. The following documents are cited in the present decision:

D1 WO-A-98/30231;

D3 Young A.A. et al., Diabetes, Vol. 48,
pages 1026-1034 (1999);

D16 American Diabetes Association, Diabetes Care,
Vol. 26, Supplement 1, pages S83-S86 (2003);

- D18 Juntti-Berggren L., et al., *Diabetes Care*,
Vol. 19, No. 11, pages 1200-1206 (1996);
- D19 Van Wijk et al., *Diabetes Care*, Vol. 28, No. 4,
pages 844-849 (2005);
- D20 Nordestgaard et al., *JAMA*, Vol. 293, No. 3,
pages 299-308 (2007);
- D21 Knapper et al., *Biochemical Society Transactions*,
Vol. 21, page 135S (1993);
- D22 Knapper et al., *J. Nutr.*, Vol. 125, No. 2,
pages 183-188 (1995);
- D23 Upton R. et al., *British Journal of Pharmacology*,
Vol. 125, pages 1708-1714 (1998);
- D24 Jodka C. et al., *Diabetes*, Vol. 47,
page 403A (1998);
- D25 Plaisance E.P. et al., *Am. J. Clin. Nutr.*,
Vol. 88, pages 30-37 (2008);
- D26 Patsch J.R. et al., *Arterioscler. Thromb. Vasc.
Biol.*, Vol. 12, pages 1336-1345 (1992);
- D27 Nikkilä M. et al., *Atherosclerosis*, Vol. 106,
pages 149-157 (1994);
- D28 Jeppesen J. et al., *Diabetes Care*, Vol. 17,
No. 10, pages 1093-1099 (1994);

- D29 Kirby R.J. et al., Journal of Lipid Research, Vol. 45, pages 89-98 (2004);
- D30 Hsieh J. et al., Diabetologia, Vol. 53, pages 552-561 (2010);
- D31 Toft-Nielsen M.-B. et al., Diabetes Care, Vol. 22, pages 1137-1143 (1999);
- D32 Rastogi V.B., Modern Biology, Pitambar Publishing Co., New Delhi, Vol. II, pages II-34 and II-35 (2004);
- D33 Declaration of Dr. Barbara Howard dated 13 February 2008.

VI. With letter dated 20 April 2012, the appellant submitted documents D25 to D32 as well as a new main request and auxiliary requests 1 to 7.

VII. Claims 1 and 12 of the main request read as follows:

"1. Use of an exendin or exendin agonist in the manufacture of a medicament for use in the treatment of hypertriglyceridemia in a human or animal subject, wherein said exendin or exendin agonist is selected from exendin-4 acid, exendin-4 (1-30), exendin-4 (1-30) amide, exendin-4 (1-28) amide, ¹⁴Leu, ²⁵Phe exendin-4, ¹⁴Leu, ²⁵Phe exendin-4 (1-28) amide, exendin-3 or exendin-4 and wherein said hypertriglyceridemia is postprandial triglyceride levels.

12. Use according to any of the preceding claims wherein the hypertriglyceridemia is in a subject with a

dyslipidemia."

Claims 2 to 11 related to specific embodiments of the use according to claim 1.

Claim 12 of auxiliary request 1 and claim 11 of auxiliary requests 2 and 3 were identical with claim 12 of the main request.

The claims of auxiliary request 4 were identical with those of the main request, except for the deletion of claim 12.

VIII. The submissions by the appellant, insofar as they are relevant to the present decision, can be summarized as follows:

Admissibility of the new main and auxiliary requests and of documents D25 to D32

- The new requests did not introduce any new matter or change the framework of the appeal proceedings. The new requests were only previous requests in modified form (see under "Article 123(2) EPC" below).
- The new requests were not filed tactically or abusively. Opponents I and II (hereinafter respondents I and II or respondents) had over four weeks in which to consider them which was sufficient time in the case of requests which did not introduce anything new.

- Document D25 was a further example (in addition to document D19) that fasting and postprandial levels of triglycerides are regulated separately. Documents D26 and D27 were referred to in the patent. Document D28 assessed the effect of metformin on postprandial lipemia. Document D29 dealt with the impact of the rate of gastric emptying on cholesterol absorption. Document D30 tried to elucidate the mechanism by which exendin-4 reduced postprandial triglycerides. Document D31 showed the possible relevance of the administration of insulin. Document D32 provided a summary of the absorption of fats in the small intestine. For these various reasons, all these documents were relevant and should be admitted.

Main request and auxiliary requests 1, 2 and 3

Article 123(2) EPC

- The new main request corresponded to auxiliary request 1 previously on file with a correction of an obvious typographical error in claim 10 (correcting "is combination" to "in combination")
- Auxiliary request 1 differed from the main request insofar as it referred to "total" postprandial triglyceride levels.
- Auxiliary requests 2 and 3 differed from the main request and auxiliary request 1, respectively, in that the feature of claim 11 had been incorporated into claim 1.

- As regards the wording "wherein the hypertriglyceridemia is in a subject with a dyslipidemia" in claim 12 (main request and auxiliary request 1) or 11 (auxiliary requests 2 and 3), hypertriglyceridemia was a specific form of dyslipidemia. Thus, the treatment of any patient suffering from hypertriglyceridemia necessarily implied the treatment of dyslipidemia at the same time.

- The skilled person would also understand from page 13, lines 5-7 and page 38, lines 6-7 of the application as filed that the lowering of other lipids, in addition to triglycerides, resulted in the treatment of both hypertriglyceridemia and dyslipidemia.

Auxiliary request 4

- Auxiliary request 4 corresponded to the main request with the further amendment that claim 12 of the main request had been deleted.

Sufficiency of disclosure (Article 83 EPC)

- There was no basis for a finding of insufficiency of disclosure since the number of possible analogues to be tested was limited to seven compounds and the biological activity could easily be tested by the skilled person.

- No substantiation by way of verifiable facts had been provided by the respondents that these seven

compounds were not effective to treat hypertriglyceridemia.

- In the situation dealt with in decision T 497/02 of 27 May 2004, none of the peptides had been tested for their biological activity. In the present case, once the present inventors demonstrated a biological effect in vivo for exendin-4, the skilled person would reasonably expect that such an effect would also be obtained for the remaining derivatives and fragments of exendin-4 and exendin-3 referred to in claim 1.
- Moreover, paragraph [0015] of the patent disclosed that exendin-3 had the same biological function as exendin-4 and document D1 provided evidence for the biological function of the exendin-4 derivatives and fragments.
- None of the exendins and exendin analogs now claimed was a truncated form of exendin-4 endowed with antagonist rather than agonist activity towards the GLP-1 receptor (see paragraphs [0016] and [0017] of the patent).

Novelty (Article 54 EPC)

- There was no unambiguous disclosure in document D3 of using exendin-4 for reducing the postprandial triglyceride levels. Document D3 merely disclosed a decrease in the fasting plasma triglyceride levels after four weeks.

- The postprandial triglyceride levels were linked neither to the fasting triglyceride levels, nor to reduced body weight or food intake.

Inventive step (Article 56 EPC)

- Document D3 represented the closest prior art. The problem to be solved was the provision of a medicament for lowering postprandial triglycerides in humans.
- From the disclosure of document D3 that exendin-4 reduced fasting triglycerides in rats, it could not be extrapolated that exendin-4 would also reduce the postprandial triglyceride levels in humans.
- The skilled person would not have assumed that a decrease in fasting triglycerides measured at 4 weeks of a 6 week treatment would mean that exendin-4 given to a subject prior to a meal would result in a reduction of the higher triglyceride levels usually seen shortly after said meal.
- To assume that the only relevant clinical marker for hypertriglyceridemia was the fasting triglyceride levels was incorrect.
- There was no teaching in document D3 that any of the several different potential mechanisms, let alone gastric emptying, was a proven mechanism controlling glycemic control and/or insulin sensitivity, let alone triglyceride levels, or

that any of these potential mechanisms could reduce postprandial triglyceride levels.

- The postprandial triglyceride levels were not linked to reduced body weight or food intake.

IX. The submissions by the respondents, insofar as they are relevant to the present decision, can be summarized as follows:

Admissibility of the new main and auxiliary requests and of documents D25 to D32

- The appellant should have made its entire case in its statement of grounds of appeal. No new claims were filed with the grounds of appeal, a main request and auxiliary request 1 were filed with the appellant's next submission of 14 December 2011, no preliminary opinion adverse to the appellant was issued by the Board, yet on 20 April 2012 - one month before the oral proceedings - the appellant filed a new main request, seven new auxiliary requests and eight new documents. The only explanation given was that they were said to be in preparation for the oral proceedings. This was improper tactics and did not allow the respondents sufficient time to prepare. Except that respondent II did not object to the admissibility of document D28, both respondents objected to the admissibility of all of documents D25 to D32.

Main request and auxiliary requests 1, 2 and 3

Article 123(2) EPC

- Claim 11 (auxiliary requests 2 and 3) or 12 (main request and auxiliary request 1) contained added subject-matter because they related to the use of specific exendins or exendin agonists for the treatment of a patient suffering from both hypertriglyceridemia and dyslipidemia, i.e. an embodiment which had no basis in the application as filed.

- The contested claims only made sense if hypertriglyceridemia and dyslipidemia were considered as two distinct clinical conditions, as suggested by the application as filed.

Auxiliary request 4

Sufficiency of disclosure (Article 83 EPC)

- Claim 1 covered derivatives and fragments of exendin-4 and exendin-3, but the patent in suit failed to provide any evidence that any of these compounds were effective to treat hypertriglyceridemia, as Example 186 of the patent only dealt with experimental data relating to exendin-4.

- Hence, the situation in the present case was similar to that dealt with in decision T 497/02, where the then competent board found insufficiency of disclosure because the skilled person had no supporting data in the application as filed and had to perform experiments to see which, if any,

of the claimed compounds had insulinotropic activity.

- Moreover, paragraphs [0016] and [0017] of the patent taught that truncated forms of exendin-4 had antagonist rather than the necessary agonist activity towards GLP-1.

Novelty (Article 54 EPC)

- Document D3 disclosed the administration of exendin-4 and the resulting statistically significant reduction of fasting triglyceride levels (page 1030, r-h column, lines 9-12 from the bottom, and r-h column, second paragraph of the discussion) in ZDF rats (an established model for diabetes). Although ZDF rats were not explicitly reported in document D3 to be hypertriglyceridemic, this was an implicit feature of this model (see document D23, page 1711, Table 2).
- As regards the feature in claim 1 "wherein said hypertriglyceridemia is postprandial triglyceride levels", it is true that the authors of document D3 measured the fasting triglyceride levels. It was the fasting plasma triglyceride level which was used by clinicians to diagnose hypertriglyceridemia. Hence, any treatment of hypertriglyceridemia sought to lower fasting plasma triglyceride concentrations and, if the fasting triglyceride levels were lowered, post-prandial triglyceride levels were also lowered.

- Moreover, the reduction in the plasma levels of the triglycerides reported in document D3 was a natural consequence of reduced body weight and food intake which was mentioned in the paper.
- Hence, claim 1 of auxiliary request 4 lacked novelty in view of document D3.

Inventive step (Article 56 EPC)

- Document D3 represented the closest prior art, as it described the plasma triglyceride lowering effect of exendin-4 in rats. The problem to be solved was the provision of a medicament for lowering plasma postprandial triglycerides in humans.
- This problem was not solved by all the exendin-4 agonists recited in claim 1, because from the data for exendin-4 it was not credible that the other compounds of claim 1 had the same effect.
- As regards exendin-4, it was obvious to the skilled person, in the light of the disclosure of document D3 that exendin-4 reduced fasting triglycerides in rats, also to try and treat postprandial hypertriglyceridemia in humans with exendin-4 with a reasonable expectation of success. This is because it was known by the skilled person at the priority date of the patent in suit that:
- The fasting triglyceride levels were the only clinically relevant marker, not the postprandial triglyceride levels.

- The reduction of fasting triglyceride levels inevitably led to the reduction of the post-prandial triglyceride levels.
 - Exendin-4 inhibited gastric emptying in rats (see document D24) and delayed gastric emptying was likely to diminish postprandial triglyceride levels due to delayed absorption of dietary triglycerides (see document D18, page 1200, r-h column).
 - The reduction in the plasma levels of the fasting triglycerides reported in document D3 was a natural consequence of reduced body weight and food intake (see document D3, page 1030, middle of r-h column).
- X. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained on the basis of its main request or on the basis of one of its auxiliary requests 1 to 7, all filed on 20 April 2012.

The respondents (opponent OI and opponent OII) requested that the appeal be dismissed.

Reasons for the Decision

Admissibility of the new main and auxiliary requests

1. There can be no dispute that these new requests were filed at a very late stage of the appeal proceedings,

i.e. only one month before the oral proceedings. The admissibility of these requests is therefore at the board's discretion (see Article 13 RPBA). Although late, the board is not satisfied that the respondents had insufficient time to consider them and to prepare their submissions for the oral proceedings. It is also pertinent in this connection that the new requests were all variations of previous requests and did not introduce any truly new matter, but only reductions in the scope of some claims and/or in the number of claims. Thus the criteria in Article 13(1) and (3) RPBA were met.

2. The respondents' argument that the appellant's entire case should have been made in its grounds of appeal is correct (see Article 12(2) RPBA) but their related supporting argument that the grounds of appeal in this case did not enclose new claims and that these were only filed with the appellant's letter of 14 December 2011 is an exaggeration. The grounds of appeal defined a new main request and auxiliary request 1 by stating that the claims of these were identical to those of previous requests filed during the opposition proceedings. The actual requests were thus readily ascertainable although not actually enclosed with the grounds of appeal. Neither respondent commented on the absence of hard copies of those requests and both filed replies presenting arguments on the requests. That the requests as such were only filed on 14 December 2011 is thus of no consequence. In effect, the appellant did file requests with its grounds of appeal which were then replaced by those filed on 20 April 2012.

Admissibility of documents D25 to D32

3. The respondents' objection to admissibility of these documents has some force. It is clear that the appellant could have filed these documents at an earlier point in time. To do so only one month before the oral proceedings clearly placed a greater burden of preparation on the respondents than they could have expected. Accordingly, the board needs to be satisfied that there are good reasons to admit such late-filed evidence.

Of the eight new documents, four were post-published (documents D25, D29, D30 and D32) and the board has no hesitation in refusing to admit these into the proceedings. They are not prior art and a persuasive case would have to be made for considering them even if filed at the proper time. Of the remaining four documents (D26, D27, D28 and D31), the board could accept that the appellant has made a case for admitting each of them on the grounds of relevance and that the respondents have not countered this with specific objections other than that of lateness. Lateness is of course a serious objection but, in the circumstances of this case, the board in its discretion gives more weight to relevance. A further factor is that no party suggested that admitting any of these documents would require an adjournment of the oral proceedings.

Additionally, documents D26 and D27 were mentioned in the patent and, although not previously relied on expressly by the appellant, were known to the respondents as documents which the appellant (as patent proprietor) considered as having some relevance to the

subject-matter of the invention. The second respondent did not object to the admissibility of document D28 and, in the absence of any specific objection by the first respondent other than late-filing, this was a factor in deciding to admit this document - parties cannot simply choose between the documents they object to or not to suit their convenience. In the result, of the eight late-filed documents, the four post-published documents were not admitted but the four prior art documents were admitted into the proceedings.

Main request and auxiliary requests 1, 2 and 3

Claim 12 (main request and auxiliary request 1) and claim 11 (auxiliary requests 2 and 3)

Article 123(2) EPC

4. These claims comprise the wording "wherein the hypertriglyceridemia is in a subject with a dyslipidemia", which the opposition division found not to add any subject-matter (see decision under appeal, point 2.1), whereas the respondents argue that this language has no basis in the application as filed (the latter is identical with the published International application WO 01/51078).
5. Owing to this expression, claims 12 or 11 at issue pertain to the treatment with the specific extendings of the invention of a patient suffering from both hypertriglyceridemia and dyslipidemia.
6. The board observes that there is no expressis verbis statement in the application as filed that a patient suffering from both hypertriglyceridemia and dyslipidemia should be treated with the specific

exendins according to the invention. Rather, page 10, lines 6-7 and page 15, line 17 of the application as filed ("as well as") and original claims 1, 19 and 24 make it clear that the patient being treated suffers from either hypertriglyceridemia or dyslipidemia, not both. Therefore, the question arises whether or not the feature in claim 1 "wherein the hypertriglyceridemia is in a subject with a dyslipidemia" can nevertheless be derived implicitly from the application as filed.

7. The appellant considers that the treatment of any patient suffering from hypertriglyceridemia necessarily implies the treatment of dyslipidemia at the same time, as hypertriglyceridemia is a specific form of dyslipidemia (see document D16 and page 5, line 4 of the application as filed).
8. However, the board notes that the application as filed provides on page 10, lines 7-8 and page 15, lines 15-19, an explicit definition of the term dyslipidemia as being "increased LDL cholesterol, increased VLDL cholesterol, and/or decreased HDL cholesterol" (in blood). A definition ("excess amount of triglycerides") of the term "hypertriglyceridemia" is also given on page 2, line 12 of the application as filed. Therefore, the application as filed does not consider hypertriglyceridemia as a specific form of dyslipidemia. As a consequence, a patient suffering from hypertriglyceridemia is not necessarily one who also suffers from dyslipidemia.
9. As for document D16 (see page S83, first column: "[T]he most common pattern of dyslipidemia in type 2 diabetic patients is elevated triglyceride levels"), cited by

the appellant to show that hypertriglyceridemia is a form of dyslipidemia, this post-published (2003) document may not reflect the common general knowledge at the priority date of the patent in suit (2000). Moreover, the board cannot ignore the fact that by conferring a specific definition on the term "dyslipidemia" as bearing exclusively on certain lipoprotein disorders (see point 8 supra), the application as filed acts as its own dictionary (see decision T 1321/04 of 28 February 2005, point 2.2 of the "Reasons"), and only the meaning given by this dictionary is ultimately decisive, not the one provided by a post-published document.

10. As for the passage on page 5, line 4 of the application as filed ("treatment of hyperlipidemia, including elevated triglycerides") emphasized by the appellant, the board notes that this passages relates to "hyperlipidemia", which is a concept different from dyslipidemia. In fact, hyperlipidemia can only relate to increased ("hyper") levels of lipids, whereas dyslipidemia may also relate to a decrease in the HDL cholesterol in blood (see point 8 supra). Therefore, the passage on page 5, line 4 of the application as filed cannot represent a basis for the wording in claim 1 "wherein the hypertriglyceridemia is in a subject with a dyslipidemia".
11. The appellant maintains that the skilled person would understand from page 13, lines 5-7 and page 38, lines 6-7 of the application as filed that the lowering of other lipids, in addition to triglycerides, resulted in the treatment of both hypertriglyceridemia and dyslipidemia.

12. As regards the passage on page 13, lines 5-7 ("In a further aspect, the modulation of lipid levels in a subject...[I]n this aspect, the lipids refer to lipids in addition to triglycerides, including, for example, cholesterols"), it cannot be derived from this passage that the patient to be treated suffers from both hypertriglyceridemia and another lipid disorder. In any case this modulation of the lipid levels referred to in this passage cannot be equated to the modulation of dyslipidemia as defined on page 10, lines 7-8 as being a lipoprotein disorder. It is merely the modulation of the levels of the lipids other than the triglycerides already mentioned on page 2, lines 3-4 of the application as filed ("phospholipids, such as lecithin and sterols, such as cholesterol"). Thus, the contested expression "wherein the hypertriglyceridemia is in a subject with a dyslipidemia" cannot be directly and unambiguously derived from this passage.

13. Finally, it cannot directly and unambiguously be derived from the passage on page 38, lines 6-7 of the application as filed ("elevated triglycerides (or other dyslipidemia) and ...the desired triglyceride (or other lipid level) is reached") that the patient to be treated suffers from both hypertriglyceridemia **and** dyslipidemia. The conjunction "or" is rather in keeping with the passages highlighted in point 6 supra, according to which the patient being treated suffers from either hypertriglyceridemia or dyslipidemia, not both.

14. In view of the foregoing, the board must conclude that the subject-matter of claim 12 (main request and

auxiliary request 1) and claim 11 (auxiliary requests 2 and 3) does not satisfy the requirements of Article 123(2) EPC. Therefore, the main request and auxiliary requests 1, 2 and 3 must fail.

Auxiliary request 4

Article 123(2) EPC

15. This claim request no longer includes the contested claim 12 comprising the wording "wherein the hypertriglyceridemia is in a subject with a dyslipidemia", found by the board to contravene Article 123(2) EPC.

Sufficiency of disclosure (Article 83 EPC)

16. It is the respondents' view that an unacceptable effort was required for the skilled person to experiment and to see which, if any, of the claimed derivatives and fragments of exendin-4 and exendin-3 could be used to treat postprandial hypertriglyceridemia, having regard to the fact that Example 186 of the patent in suit showed merely that exendin-4 exhibited this biological activity.
17. In the board's view, however, this argument is not convincing. It is undisputed that Example 186 of the patent illustrates the ability of exendin-4 to lower triglycerides in humans (see page 73 of the patent). This study compares the effects of multiple dosing of synthetic exendin-4 and placebo given twice daily for five days. The above treatment results in a significant reduction of postprandial circulating triglycerides (see page 73, lines 33 and 34 of the patent).

Specifically, peak postprandial triglyceride concentrations were reduced by 24% compared to placebo (see page 73, lines 38-39 of the patent).

18. During the oral proceedings the appellant argued that the patent in suit (see paragraph [0015]) and the data disclosed in D1 made it moreover plausible for the skilled person that the other compounds recited in claim 1 exhibited the same biological properties as exendin-4. Document D1 shows that exendin-4 derivatives exendin-4 (1-30); exendin-4 (1-30) amide; exendin-4 (1-28) amide; ¹⁴Leu, ²⁵Phe exendin-4 amide; ¹⁴Leu, ²⁵Phe exendin-4 (1-28) amide reduce food intake in mice (see Example 4 and Figures 4 to 8 of document D1). The patent discloses that exendin-3 stimulates cAMP production in, and amylase release from, pancreatic acinar cells (see paragraph [0015] of the patent). In view of this evidence the board is satisfied that the skilled person would have considered it plausible that the claimed exendin agonists have the same effect as exendin-4 in the treatment of postprandial hypertriglyceridemia.

19. The respondents maintain that the situation in the present case is similar to that dealt with in decision T 497/02. In that case, the then competent board concluded (see points 17 and 18 of the Reasons) that the skilled person, when trying to carry out the claimed invention, had to produce 31 GLP-1(7-37) peptides lacking one amino acid at each position between 7 and 37 (the "minus-one GLP-1(7-37) peptides"), and to perform tests to determine whether they possessed the required biological activity. However, the then competent board considered that this research

program had to be performed with **no certainty of even a single success**, since it was common general knowledge that the internal deletion of a single amino acid could have a great influence on the secondary and tertiary structure and the three-dimensional folding of a peptide, and hence on the biological activity.

20. In the present case, no internal deletions of amino acids have been made in the exendin agonists referred to in present claim 1, but only substitutions and C-terminal truncations. Moreover, these exendin-4 agonists are known to keep a series of biological activities of exendin-4 (see point 18 above). Thus the board cannot agree with the respondents that the situation in the present case is similar to that dealt with in decision T 497/02.
21. The respondents also maintain that, according to paragraphs [0016] and [0017] of the patent, truncated forms of exendin-4 have antagonist rather than agonist activity towards the human GLP-1 receptor. Hence, the patent disclosure itself raises serious doubts about the effectiveness of the untested compounds to treat postprandial hypertriglyceridemia.
22. The board observes that paragraphs [0016] and [0017] of the patent disclose that truncated exendin molecules such as exendin-4 [9-39] and [3-39] through [9-39] act as antagonists of GLP-1. Although these truncations are denoted as "C-terminal" in paragraph [0017] of the patent, the skilled person would have immediately understood - in view of the disclosed residue numbering- that the truncations are in fact situated at the N-terminus. Since the claimed exendin-4 fragments

are truncated at the C-terminus, paragraphs [0016] and [0017] of the patent cannot therefore be considered as raising serious doubts about the activity of the claimed fragments.

23. For the above reasons, the arguments provided by the respondents are not convincing and the claims are found to fulfill the requirements of Article 83 EPC.

Novelty (Article 54 EPC)

24. Claim 1 is directed to the "treatment of hypertriglyceridemia wherein said hypertriglyceridemia is postprandial triglyceride levels". Document D3 has been cited against the novelty of the subject-matter of this claim.
25. Document D3 is silent about postprandial triglyceride levels. Rather, the authors of document D3 observed a decrease in fasting plasma triglycerides after four weeks (see page 1030, l-h column, end of penultimate paragraph and r-h column, third full paragraph). However, the respondents argue that the reduction of fasting triglyceride levels inevitably leads to a reduction of postprandial triglyceride levels and that document D3 therefore implicitly discloses the subject-matter of claim 1.
26. The board observes that document D26 (see page 1337, l-h column, second full paragraph) shows that fasting triglyceride levels and postprandial triglyceride levels are regulated by different mechanisms. Post-published document D19 (see page 846, middle of r-h column) reports that: "[T]he data from the present

study show that rosiglitazone does not change fasting triglycerides but decreases the postprandial triglyceride increase in plasma (-37%)..." and thus confirms this finding. In conclusion, high (or low) levels of fasting triglycerides do not necessarily imply high (or low) postprandial triglyceride levels, and vice-versa.

From document D26 it can also be understood that fasting triglyceride levels and postprandial triglyceride levels were considered by clinicians as separate disease markers (see document D26, page 1336, lines 7 to 11 from the bottom of the abstract, and the further scientific literature cited in paragraph [0011] of the patent in suit).

27. The respondents further argue that according to document D3 (see page 1030, middle of r-h column) exendin-4 treatment was associated with a decrease in fasting triglycerides, a reduction in food intake, and a reduction in body weight and that - as was derivable from document D33 (see page 7, end of point 23) - the reduction in food intake inevitably resulted in reduced postprandial triglyceride levels. Hence, for this reason also, document D3 anticipated the subject-matter of claim 1.

28. However, when read in context the passage of document D33 relied on by the respondents has to be understood as relating to fasting triglyceride levels only, which levels are not linked to postprandial triglyceride levels (see point 26).

29. Thus, the arguments provided by the respondents are not convincing. Consequently the claims are considered to fulfill the requirements of Article 54 EPC.

Inventive step (Article 56 EPC)

Closest prior art

30. Document D3 is a publication by one of the two inventors of the patent in suit, dealing with the effects of exendin-4 on the glucose levels in various animals. It also reports that in ZDF diabetic rats (an established model for studying diabetes), plasma concentrations of fasting (baseline) triglycerides were significantly reduced at all doses by between 51 and 65% (see page 1030, left column, end of penultimate paragraph and right column, under "Discussion", second paragraph). The fasting triglycerides began to decrease 2 weeks before the end (see page 1030, left column, lines 14-15 from the bottom) of a 5-6 week treatment (see Abstract). Therefore, document D3 represents the closest prior art.

Problem to be solved

31. The problem to be solved is the provision of a medicament for lowering plasma postprandial triglycerides in a human or animal subject. The solution to this problem is either exendin-4 or one of the seven exendin-4 agonists listed in claim 1.
32. The respondents argue that the problem was not solved by all the exendin-4 agonists recited in claim 1. However, the board has found that all claimed compounds can reasonably be considered to have the capability of

- lowering plasma postprandial triglycerides in a human or animal subject (see point 18 above). The board is therefore satisfied that the problem has been solved.
33. The relevant question to be answered in the context of inventive step is whether or not the above solution follows from the prior art in an obvious way.
34. In item 4.4 of the decision under appeal, the opposition division concluded that:
- "From D3, the skilled person would also deduct that if one can reduce fasting triglyceride levels (i.e. baseline), then one would also reduce postprandial triglyceride levels by means of the same treatment, since the only relevant clinical levels for hypertriglyceridemia are the fasting levels, and there is no real medical distinction between the reduction of fasting triglycerides and that of post-prandial triglycerides."*
35. The respondents also argue along that line.
36. However, as already mentioned in the context of novelty, fasting triglyceride levels and postprandial triglyceride levels are separate disease markers and are regulated by independent mechanisms (see point 26 above). Contrary to the respondents' contention, high (or low) levels of fasting triglycerides do not therefore necessarily imply high (or low) postprandial triglyceride levels, and vice-versa.
37. The opposition division also relied on the passage of document D3 (see page 1030, r-h column, lines 14-15

- from the bottom), according to which exendin-4 induces "a slowing of gastric emptying". The opposition division combined this passage with that on page 1200, r-h column of document D18, disclosing that "the gastrointestinal motility is decreased, which is likely to diminish postprandial triglyceridemia due to delayed absorption of dietary triglycerides", to conclude that the teaching in document D3 was a clear pointer towards the claimed medical use.
38. However, in the board's view, the wording "a slowing of gastric emptying" in document D3 is merely mentioned as one of the possible mechanisms responsible for the improvement in glycemic control and insulin sensitivity (see page 1030, r-h column, line 17 from the bottom), but not for that underlying elevated triglyceride levels. Moreover, the passage in document D18 is concerned with the anti-diabetogenic effect of GLP-1 (D18, page 1204, first sentence of conclusions), which was known at the priority date to have different physiological effects as compared to exendin-4. For example, GLP-1 had no effect on triglyceride levels (see document D31, page 1140, l-h column, first full paragraph).
39. Therefore, the board is not persuaded that the skilled person would have actually combined these passages from documents D3 and D18 in the expectation that exendin-4 would be useful for treating postprandial hypertriglyceridemia.
40. Finally, the respondents maintain that the disclosure in document D3 of a reduction in the plasma levels of the fasting triglycerides by exendin-4 would suggest to

the skilled person a concomitant reduction in postprandial triglyceride levels (see document D3, page 1030, middle of r-h column).

41. However, in the board's view, this passage in document D3 relates to the fasting triglycerides levels and the skilled person knew at the effective date of the patent in suit that fasting triglycerides levels and postprandial triglycerides levels are regulated by different mechanisms (see point 26 supra).

42. Therefore the board concludes that the subject-matter of claim 1 does not follow from the prior art in an obvious way. This also applies to claims 2 to 11 which are all dependent on claim 1. Hence, 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 auxiliary request 4 filed on 20 April 2012 and a description and figures to be adapted thereto.

The Registrar:

The Chairman:

D. Magliano

C. Rennie-Smith