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Datasheet for the decision of 15 November 2018

Case Number: T 1427/14 - 3.3.04

Application Number: 06727006.6

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Language of the proceedings: EN

Title of invention:
Glucagon-like-peptide-2 (GLP-2) analogues

Patent Proprietor:
Zealand Pharma A/S

Opponent:
Shire - NPS Pharmaceuticals, Inc.

Headword:
GLP-2 analogues/ZEALAND

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13

Keyword:
Main request: inventive step (yes)

Decisions cited:

Catchword:

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Case Number: T 1427/14 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 15 November 2018

Appellant: (Opponent)	Shire - NPS Pharmaceuticals, Inc. 550 Hills Drive, 3rd Floor Bedminster, NJ 07921 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Patent Proprietor)	Zealand Pharma A/S Smedeland 26B 2600 Glostrup (DK)
Representative:	Forrest, Graham Robert Mewburn Ellis LLP City Tower 40 Basinghall Street London EC2V 5DE (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 June 2014 rejecting the opposition filed against European patent No. 1877435 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chair	G. Alt
Members:	R. Morawetz
	P. de Heij

Summary of Facts and Submissions

I. The appeal of the opponent ("appellant") lies from the decision of the opposition division rejecting the opposition filed against European patent No. 1 877 435, entitled "*Glucagon-like-peptide-2 (GLP-2) analogues*".

II. The patent had been opposed under Article 100(a) EPC on the ground of lack of inventive step (Article 56 EPC) and under Article 100(b) and (c) EPC.

III. In its statement of grounds of appeal, the appellant provided arguments against the decision of the opposition division as regards added subject-matter, sufficiency of disclosure and inventive step of the claims as granted.

IV. In reply to the statement of grounds of appeal, the patent proprietor ("respondent") submitted auxiliary requests 1 to 11 and provided arguments regarding the patentability of the set of claims as granted.

V. The board issued a summons to oral proceedings accompanied by a communication pursuant to Article 15(1) RPBA setting out its preliminary opinion as regards the added subject-matter objection to position X31 of the GLP-2 analogues of claim 1 as granted; the sufficiency objections against claims directed to "gene-therapy"-type applications; and inventive step and sufficiency objections regarding the generic formulae from the granted claims. No time limit for filing further written submissions was set by the board.

VI. In reply, the respondent filed a corrected version of auxiliary request 4 and an auxiliary request 12 as well

as arguments as regards admissibility and patentability of the set of claims of auxiliary request 12.

VII. During the oral proceedings, the respondent promoted auxiliary request 12 to its main request and renumbered the pending claim requests accordingly.

Independent claims 1 to 3 of the main request read:

"1. A GLP-2 analogue which is:

1846 H-HGEGSFSSELSTILDALAARDFIAWLIATKITDKKKKKK-NH2;
or a pharmaceutically acceptable salt thereof.

2. A GLP-2 analogue which is:
1848 H-HGEGTFSSELATILDALAARDFIAWLIATKITDKKKKKK-NH2;
or a pharmaceutically acceptable salt thereof.

3. A GLP-2 analogue which is:
1844 H-HGEGTFSSELSTILDALAARDFIAWLIATKITDKKKKKK-NH2;
1849 H-HGEGSFSSELATILDALAARDFIAWLIATKITDKKKKKK-NH2;
1852 H-HGEGTFSSELKTILDALAARDFIAWLIATKITDKKKKKK-NH2;
1853 H-HGEGTFSSELSTILDALAARDFIAWLIATKITD-NH2;
1855 H-HGEGSFSSELSTILDALAARDFIAWLIATKITD-NH2;
1857 H-HGEGTFSSELATILDALAARDFIAWLIATKITD-NH2;
1858 H-HGEGSFSSELATILDALAARDFIAWLIATKITD-NH2;
or a pharmaceutically acceptable salt thereof."

Claims 4 to 27 of the main request are directed to various medical uses of the GLP-2 analogues of claims 1 to 3, pharmaceutical compositions and therapeutic kits comprising the GLP-2 analogues of claims 1 to 3, nucleic acid molecules encoding GLP-2 analogues of claims 1 to 3, expression vectors comprising these nucleic acid molecules and host cells transformed with these expression vectors.

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

VIII. The following documents are referred to in this decision:

D1 WO 97/39031 (1997)

D2 DaCambra M.P. *et al.*, Biochemistry (2000), Vol. 39, pages 8888 to 8894

D3 US 2004/0122210 (2004)

D12 Amended version of Table 15 of the patent, including the correct column headings, filed by letter dated 14 January 2014

D13 Table summarising selected data from document D1, filed during the oral proceedings before the opposition division

IX. The arguments of the appellant, submitted in writing and during the oral proceedings, may be summarised as follows:

Main request

Admissibility into the appeal proceedings

The request combined the amendments made in previous auxiliary requests 1 and 11, but no substantiation had been provided when these requests had been filed.

The objections as regards added subject-matter and sufficiency of disclosure were addressed by this

request, but the issue of inventive step required further discussion.

Accordingly, it was not clear on the face of it that this request overcame all outstanding objections or advanced procedural economy. Clear allowability was in any case only one of the criteria to be considered.

If the request was filed in response to the board's communication, it could have been filed sooner and not four months after receiving the communication and thus only two months before the oral proceedings.

Making auxiliary request 12 the main request in the oral proceedings constituted filing a new request at a late stage.

The reshuffled claim requests - as a whole - did not converge.

The request should not be admitted into the appeal proceedings.

Inventive step (Article 56 EPC)

Closest prior art

Document D1, which disclosed various glucagon-like-peptide-2 (GLP-2) analogues having intestinotrophic activity, was the closest prior art. It provided a general formula on page 3 allowing for many replacements. All compounds disclosed in Table 1 of document D1 had intestinotrophic activity.

Technical problem and its solution

The subject-matter of claims 1 to 3 related to GLP-2 analogues and was not limited by any particular use, e.g. a pharmaceutical use. The claimed compounds had to be compared to all the compounds of document D1, not only to the compound [Gly2]hGLP-2.

It was not contested that the data in the patent showed that the claimed compounds showed an improved effect on intestinal growth over [Gly2]hGLP-2. However, since no comparison with other compounds had been provided, it could not be concluded that the claimed compounds were better than all compounds in document D1. Contradictory results were reported in Tables 1 and 2 of document D1 for compound 21.

The problem to be solved was to provide alternative GLP-2 analogues which exerted biological activity, e.g. as research tools.

Obviousness

The claimed analogues were obvious from document D1 in combination with the teaching of documents D2 or D3.

Amino acid positions 3, 10, 16, 24 and 28 of GLP-2 had already been identified for substitutions in document D1. Thus, on page 10, line 19, Glu3 (i.e. a GLP-2 analogue having glutamic acid at position 3) and, in line 25, Leu10 were disclosed. In Example 5, in Table 2, Ala24, Ala16 and Ala28 were disclosed. The claimed substitutions at all these positions were thus obvious. Therefore, combinations of these substitutions were obvious as well.

Only the substitution of Asp by Ser at position 8 of GLP-2 was not disclosed in document D1. However, documents D2 and D3 would have prompted mutating position 8 to Serine.

The skilled person wanting to provide GLP-2 analogues for use as research tools in species other than mammals would have turned to document D3. This document disclosed in Figure 3 that, while mammalian GLP-2 had Asp in position 8, other animals, *e.g.* chickens, frogs, and trout had Ser. This would have prompted the skilled person to replace Asp with Ser at position 8.

Document D2 showed that residue 8 of other glucagon-related peptides was Ser.

Since the modifications at the claimed positions were obvious, the pharmaceutical effect was a bonus effect.

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

Main request

Admissibility into the appeal proceedings

This request had been filed as auxiliary request 12 well in advance of the oral proceedings in response to comments in the board's communication and had at the same time been substantiated. It combined the amendments from previously filed auxiliary requests 1 and 11 and was further restricted to specific molecules tested *in vivo*.

The claims of this request were clearly allowable and complied with the criteria set out in the case law for admissibility of late-filed requests.

The amendments raised no new issues and simply limited the claimed subject-matter to preferred embodiments clearly described in the patent and set forth in the dependent claims as granted. The appellant was thus not taken by surprise.

Admissibility was not precluded by the mere fact that some objections were outstanding and needed to be discussed.

Its promotion to the main request at the oral proceedings did not affect its content or the nature of the objections it overcame.

Convergence could not be an issue since, if this request fell, all other requests would fall too.

The request served procedural economy since it eliminated as many objections as possible.

For all these reasons, the main request should be admitted.

Inventive step (Article 56 EPC)

Closest prior art

Document D1 was the closest prior art. It disclosed analogues of GLP-2 which retained or had enhanced intestinotrophic activity. Examples 4 and 5 of document D1 illustrated the intestinotrophic activity of various GLP-2 variants; reference was made to the

summary provided in document D13. The most effective compound tested in document D1 was [Gly2]hGLP-2, as indicated on page 26, line 35. It could be seen that introducing a substitution at positions 8, 16, 28 of GLP-2 reduced the activity compared to that seen with [Gly2]hGLP-2.

Technical problem and its solution

The claimed compounds had 7 or 8 substitutions compared to the reference compound [Gly2]hGLP-2. All had substitutions at positions 3, 8, 10, 16, 24 and 28, namely, Glu3, Ser8, Leu10, Ala16, Ala24, Ala28, with different combinations of residues at positions X5 and X11.

Although no effect was recited in claims 1 to 3, all the claimed compounds had been shown to increase trophic activity on the small intestine (SI) as compared to [Gly2]hGLP-2, and increase selectivity for the SI in mammals, as followed from Table 15 of the patent and document D12. This effect (in mammals) had to be taken into account when formulating the objective technical problem. It was the purpose these peptides had been made for.

All compounds were better than [Gly2]hGLP-2 which was the compound with the highest activity of document D1.

Contradictory results were reported for compound 21, [Gly2, Ala24]hGLP-2, in Tables 1 and 2 of document D1 in that its activity was reported to be greater than [Gly2]hGLP-2 in Table 1 but smaller in Table 2. In Table 1 data were not normalised while in Table 2 they

were calculated relative to rat GLP-2. However, this difference could not account for the observed discrepancy. Compound 21 should therefore be ignored.

The problem to be solved was the provision of GLP-2 analogues with an improved effect on small bowel weight and improved selectivity for the SI over colon in mammals.

Obviousness

Document D1 showed that introducing Ala at position 8, 11, 16, 24 or 28 individually reduced the intestinotrophic effect of [Gly2]hGLP-2, as followed from the summary of the relevant data in document D13.

Thus, it would not have led the skilled person to reasonably expect that introducing mutations at these positions (whether Ala, or other substituents) would provide a molecule that was superior *in vivo* to the reference compound.

The skilled person might well have considered exchanging residues between peptides which were functionally equivalent or interchangeable. However, the other glucagon-related peptides disclosed in document D2 were not interchangeable with GLP-2, as (i) they did not possess intestinotrophic activity, and (ii) they acted at different receptors (page 8891, right hand column, penultimate paragraph). Thus, none of the peptides having Ser8 had agonist activity at the GLP-2 receptor. Consequently, the skilled person would have been inclined to avoid a substitution which would increase similarity to molecules which lack GLP-2 agonist activity and intestinotrophic activity.

As to GLP-2 molecules from other species, Figure 3 of document D3 provided an alignment of GLP-2 sequences from eight mammalian species and four non-mammalian species. Asp8 was completely conserved in all of the mammalian sequences. This provided a further disincentive for the skilled person to modify this position. There was no guarantee that a GLP-2 molecule with Ser8 would be functional at a mammalian GLP-2 receptor.

A notion of a "bonus effect" only applies when the skilled person would have been in a one-way-street situation. In the present case, there would have been no such one-way-street situation leading to the claimed molecules because the combined substitutions were individually detrimental.

XI. The appellant requested 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 sets of claims of the main request, filed as auxiliary request 12 with the letter dated 13 September 2018 or, alternatively, on the basis of the sets of claims of auxiliary request 1 (the claims of the patent as granted); the sets of claims of auxiliary requests 2 to 4, filed as auxiliary requests 1 to 3 with the letter dated 25 February 2015; the set of claims of auxiliary request 5, filed as corrected auxiliary request 4 with the letter dated 13 September 2018; or the sets of claims of auxiliary requests 6 to 12, filed as auxiliary requests 5 to 11 with the letter dated 25 February 2015.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

Main request

Admissibility into the appeal proceedings

2. This request had originally been filed as auxiliary request 12, two months before the date of the oral proceedings, in response to the board's preliminary opinion set out in a communication accompanying the summons to oral proceedings (see section V).

   It combines the amendments made in previously filed auxiliary requests 1 and 11 and is further restricted to specific compounds for which *in vivo* data are provided in the patent. In fact, the amendments limit the claimed subject-matter to preferred embodiments set forth in the dependent claims as granted.

3. Substantiation for the claimed subject-matter was provided when the request was filed as auxiliary request 12, i.e. two months before the hearing, leaving a time span which the board considers adequate for the appellant and the board to consider the request in view of the nature of the amendments.

4. By promoting auxiliary request 12 to the main request on the day of the oral proceedings, its content did not change.

5. Moreover, the amended claims were clearly allowable in that they did not give rise to new objections, overcame the objections addressed in the board's communication and allowed inventive step to be assessed without giving rise to any difficulty or delay (see also Case Law of the Boards of Appeal of the European Patent Office, 8th edition 2016, IV.E.4.4.2).

In fact, the appellant, when asked during the oral proceedings, conceded that the request addressed all outstanding objections under the EPC, except inventive step.

6. Admitting the request and dealing with it as the main request therefore served procedural economy since it limited the discussion at the oral proceedings to the issue of inventive step.

7. Finally, the fact that the claim requests, as a whole, were not convergent after the promotion of auxiliary request 12 to the main request was no bar to admitting the main request because, if this request, which was the most limited request, fell, all other requests would fall too, rendering any issue with lack of convergence moot.

8. The board is aware of case law holding that a communication by the board that contains a preliminary opinion based solely on the issues raised by the parties and their arguments, as in the present case, cannot be taken as justification for submitting new requests that the parties could have filed earlier (*ibid.*, IV.E.4.4.12).

9. However, the board considered that, taking into account the relevant circumstances of the present case (see

points 2 to 7), these circumstances justified to admit the new request into the appeal proceedings.

10. Therefore, the board, exercising its discretion pursuant to Article 13(1) RPBA, decided to admit the main request into the appeal proceedings.

Inventive step (Article 56 EPC)

11. This decision deals with the issue of whether the claimed subject-matter involves an inventive step, given that the appellant did not maintain any other objection under the EPC against the subject-matter of the claims of this request at the oral proceedings.

Closest prior art

12. The claimed invention concerns human glucagon-like-peptide-2 (hGLP-2 or GLP-2) analogues.

13. Human GLP-2 is a known 33 amino acid-long gastrointestinal hormone that regulates epithelial growth in the intestine, i.e. has intestinotrophic activity. It binds to a single G protein-coupled receptor, termed GLP-2R. It is also known that dipeptidylpeptidase IV (DPP IV) cleaves GLP-2 at the alanine at position 2, resulting in the inactivation of the peptide, and that the substitution of alanine with glycine in position 2 of GLP-2 renders the resulting peptide ([Gly2]GLP-2) DPP IV-resistant and enhances its biological effectiveness *in vivo* (see document D2, abstract, page 8889, left-hand column, first paragraph).

14. The parties agreed that document D1 represents the closest prior art. The board sees no reason to disagree.

15. Document D1 discloses analogues of GLP-2 with intestinotrophic activity. A generic formula for such GLP-2 analogues, illustrating the positions of possible amino acid replacements compared to the native GLP-2 sequence and possible replacement amino acids, is depicted on page 3, lines 1 to 24.

According to document D1, the effect on the growth of tissue of the small bowel elicited by GLP-2 analogues can be assessed in a murine model and manifests itself as an increase in small bowel weight, relative to a mock-treated control (see page 5, lines 22 to 27 and Examples 4 and 5).

In Example 4, mice were injected subcutaneously with GLP-2 analogues in phosphate buffered saline and sacrificed 10 or 14 days after injection. The small bowel (small intestine) was removed from the peritoneal cavity, from pylorus to cecum, and the percentage change in small bowel weight was calculated relative to mice treated with buffer only. The results, in terms of % increase in small bowel weight, are shown in Table 1. In the discussion of the results, the compound [Gly2]hGLP-2 is said to have a substantially increased intestinotrophic activity compared to the naturally occurring molecule (see page 24, lines 15 to 16).

In Example 5, experiments assessing the small bowel weight-inducing activity of various GLP-2 analogues were repeated as described for Example 4. The small bowel weight-inducing activity of each GLP-2 analogue was calculated relative to that of native rat GLP-2

(expressed as 100% activity), and the results were given in Table 2. According to this table, [Gly2]hGLP-2 has the highest activity relative to rat GLP-2, namely, 300%, while GLP-2 analogues carrying the glycine substitution at position 2 (Gly2) and a further substitution at, for example, position 8, 11, 16, 24 or 28 have respectively 120%, 150%, 130%, 139% and 130% activity relative to rat GLP-2.

Technical problem and its solution

16. The GLP-2 analogues recited in claims 1 to 3 differ from the GLP-2 analogues disclosed in document D1 in the amino acids glutamic acid, serine, leucine at positions 3, 8 and 10, respectively, and alanine at positions 16, 24 and 28 (Glu3, Ser8, Leu10, Ala16, Ala24, and Ala28) with different combinations of residues at positions 5 and 11 of GLP-2.

17. The respondent submitted that the technical effect associated with this difference was derivable from the patent and that it was two-fold, i.e. a superior trophic activity on the small intestine (SI) and improved selectivity for SI over colon in mammals compared to [Gly2]hGLP-2.

18. In Example 8 of the patent, the ability of several GLP-2 analogues to stimulate growth of the SI and the colon was determined in mice. The small intestine (from the pylorus to the cecum) and the colon (intestine distal to cecum) were emptied and weighed and the SI-colon sensitivity index for the compounds was calculated. The results are depicted in Table 15 of the patent. In this table, the column headings are missing. Document D12 provides an amended version of Table 15 of the patent, including the correct column headings

consistent with the definitions in paragraphs [0176] and [0177] of the patent. It was undisputed between the parties, and the board agrees, that document D12 does not add to the teaching of the patent.

Thus, the patent indeed discloses that the claimed GLP-2 analogues have a greater absolute effect on SI weight than does the reference molecule, [Gly2]hGLP-2, and that they also have a preferential growth promoting activity for SI over colon in mice as compared to [Gly2]hGLP-2 (see compounds 1846, 1848, 1844, 1849, 1852, 1853, 1855, 1857 and 1858 of Table 15 as depicted in document D12).

19. The appellant did not contest that these effects were shown in Table 15 but submitted that as claims 1 to 3 were directed to products and not limited to any particular use thereof, these effects could not be considered when formulating the objective technical problem to be solved, which could thus be seen as the provision of alternative GLP-2 analogues which exerted biological activity, e.g. as research tools.

20. However, according to established jurisprudence in relation to the assessment of inventive step in the problem and solution approach, any effect (or effects) achieved by the claimed invention compared with the closest state of the art, which is derivable from the application in the light of the common general knowledge, is taken into account for the definition of the technical problem. Therefore, the appellant's formulation of the problem cannot be accepted.

21. The appellant further submitted that no improvement for the claimed compounds over all GLP-2 analogues disclosed in document D1 could be acknowledged as the

claimed compounds had been compared solely to [Gly2]hGLP-2 but not to any other compound disclosed in document D1.

22. However, [Gly2]hGLP-2, with a 300% activity relative to rat GLP-2, is the compound with the highest small bowel weight-inducing activity according to Table 2 of document D1 (see page 26, line 35). All claimed compounds have a higher intestinotrophic activity than this compound, [Gly2]hGLP-2, which was taken as the reference compound in Table 15 of the patent (see point 19 above). Accordingly, the claimed compounds also have, *a fortiori*, a higher intestinotrophic activity than all other GLP-2 analogues disclosed in document D1 in Table 2.

23. As set out above, document D1 assessed the intestinotrophic activity of the GLP-2 analogues in two experiments in mice. For Example 4, the results are depicted in terms of % increase in small bowel weight in Table 1 (absolute activity). For Example 5, the results are depicted as % activity relative to that of native rat GLP-2 (expressed as 100% activity) in Table 2 (relative activity).

The appellant pointed out that, compared to the compound [Gly2]hGLP-2 of document D1, the compound [Gly2, Ala24]hGLP-2 had a lower relative activity (see Table 2) but a higher absolute activity (see Table 1, compounds 6 and 21).

However, in the board's opinion, the skilled person would have noted this inconsistency and would have also understood that it could not be due to the different calculation of the activity (relative versus absolute activity). Therefore, they would have concluded that

the activity of compound 21 was incorrectly indicated in one of the two tables of document D1. Not knowing which table reported the correct activity, the skilled person would have ignored the data for compound [Gly2, Ala24]hGLP-2 in both tables.

24. The board thus accepts that the claimed compounds have a higher intestinotrophic activity than the GLP-2 analogues disclosed in document D1.

25. Selectivity for SI over colon was not tested for the GLP-2 analogues in document D1. Thus, it does not automatically follow from the fact that [Gly2]hGLP-2 is the compound of document D1 with the highest intestinotrophic activity that it is also the one with the highest selectivity for SI over colon. Therefore, it can also not be concluded that the claimed compounds - which have a higher selectivity for SI over colon than [Gly2]hGLP-2 (see point 18) - have a higher selectivity for SI over colon than all GLP-2 analogues disclosed in document D1.

26. Given the foregoing, the objective technical problem to be solved is the provision of GLP-2 analogues with an improved effect on small bowel weight in mammals.

Obviousness

27. In document D1, the intestinotrophic activity of hGLP-2 analogues having alanine substitutions at various positions was studied in the context of the [Gly2]hGLP-2 structure. While [Gly2]hGLP-2 had a 300% relative activity compared to rat GLP-2, compounds having an alanine at position 8, 11, 16, 24 or 28, *i.e.* compounds [Gly2,Ala8]hGLP-2, [Gly2,Ala11]hGLP-2, [Gly2,Ala16]hGLP-2, [Gly2,Ala24]hGLP-2 and

[Gly2,Ala28]hGLP-2 had between 120% and 150% relative activity compared to rat GLP-2 (see document D1, page 26, lines 16, 17, 19, 28, 32 and 35).

Document D1 already concludes that, depending on the substitution made, various levels of intestinotrophic activity are manifest. However it does not provide any guidance as to which substitutions would reliably achieve an intestinotrophic activity even higher than that found with [Gly2]hGLP-2 (see page 24, lines 13 to 16).

28. Therefore, when faced with the technical problem formulated above in point 26, the skilled person would not have been motivated on the basis of the teaching of document D1, which discloses that introducing alanine at position 16, 24 or 28 individually reduces the intestinotrophic activity compared to [Gly2]hGLP-2, to provide a [Gly2]hGLP-2 compound with alanine substitutions at any of these positions, let alone in combination.

29. As regards other teachings in the prior art that might have provided an incentive for the skilled person to change the [Gly2]hGLP-2 sequence, documents D2 and D3 were relied on by the appellant.

30. In document D2, an alanine substitution scan of the hGLP-2 molecule was carried out to understand the specific structural determinants important for hGLP-2 binding and receptor activation (see page 8889, left-hand column, second paragraph). Document D2 also provides an alignment of the amino acid sequence of hGLP-2 and that of other glucagon-related proteins (see

Figure 1). While hGLP-2 has an aspartic acid at position 8, GLP-1, glucagon, GIP and exendin-4 have a serine at position 8 (see Figure 1).

31. However, document D2 also discloses that none of the glucagon-related peptides having serine at position 8 has agonist activity at the GLP-2 receptor (see document D2, page 8891, right-hand column, penultimate paragraph). The board agrees with the respondent that, while the skilled person might have considered exchanging amino acid residues between peptides which are functionally equivalent, they would have been reluctant to introduce substitutions into hGLP-2 which increase the similarity to molecules which lack GLP-2 agonist and thus intestinotrophic activity. Thus, the teaching of document D2 would not have provided any incentive for the skilled person, when faced with the problem recited above, to change aspartic acid to serine at position 8 of hGLP-2.

32. Document D3 provides an alignment of the amino acid sequences of GLP-2 from eight mammalian and four non-mammalian species (see Figure 3). It can readily be seen that the aspartic acid at position 8 is completely conserved in all of the mammalian amino acid sequences while the GLP-2 of chicken, frog, salamander and trout have serine at position 8. In the board's opinion, the complete conservation of aspartic acid at position 8 in GLP-2 sequences of mammals would have dissuaded the skilled person, when faced with the problem recited above, from introducing a serine substitution at position 8 based on GLP-2 sequences from non-mammalian species because of the concern that a GLP-2 molecule with serine at position 8 would not be functional at a mammalian GLP-2 receptor.

33. Therefore, starting from the GLP-2 analogues disclosed in document D1, the skilled person would have found neither in document D1 taken alone or in combination with the teaching of documents D2 and D3 an incentive to change positions 3, 5, 8, 10, 11, 16, 24 and 28 of hGLP-2 - let alone to make the claimed substitutions at these positions - to provide GLP-2 analogues with an improved effect on small bowel weight in mammals.

34. Accordingly, the appellant's argument that the improved intestinotrophic effect of the claimed hGLP-2 analogues was a bonus effect cannot be accepted.

35. The board concludes that the subject-matter of claims 1 to 3 is not obvious and meets the requirements of Article 56 EPC. The subject-matter of claims 4 to 27 derives its inventive step by virtue of being directed to specific embodiments involving the GLP-2 analogues of claims 1 to 3.

36. Since the respondent's main request meets the requirements of the EPC, there is no need to consider any of the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent with the following claims and a description and drawings to be adapted thereto:

   claims 1 to 27 of the main request, filed as auxiliary request 12 with the letter of 13 September 2018.

The Registrar: The Chair:

S. Lichtenvort G. Alt

Decision electronically authenticated