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Datasheet for the decision of 19 January 2017

Case Number: T 1006/12 - 3.3.04

Application Number: 03762471.5

Publication Number: 1525219

IPC: C07K14/575, C07K14/605, A61K38/26, A61P3/10

Language of the proceedings: EN

Title of invention:
GLP-1 and methods for treating diabetes

Patent Proprietor:
ZP Holding SPV K/S

Opponents:
F.Hoffmann-La Roche AG
Novo Nordisk A/S

Headword:
Drug holiday regimen/ZP HOLDING

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12(4)

Keyword:
Inventive step - (no)

Decisions cited:

Catchword:

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Case Number: T 1006/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 19 January 2017

Appellant I: (Patent Proprietor)	ZP Holding SPV K/S Smedeland 36 2600 Glostrup (DK)
Representative:	Kiddle, Simon John Mewburn Ellis LLP City Tower 40 Basinghall Street London EC2V 5DE (GB)
Appellant II: (Opponent 01)	F.Hoffmann-La Roche AG 124 Grenzacherstrasse 4070 Basel (CH)
Representative:	Jaenichen, Hans-Rainer Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Appellant III: (Opponent 02)	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd (DK)
Representative:	Probert, Gareth Potter Clarkson LLP The Belgrave Centre Talbot Street Nottingham NG1 5GG (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 April 2012 concerning maintenance of the European Patent No. 1525219 in amended form.**

Composition of the Board:

Chairman	B. Claes
Members:	A. Chakravarty
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. Appeals were lodged by the proprietor, opponent 01 and opponent 02 (appellants I, II and III, respectively) against the interlocutory decision of the opposition division that European patent EP-1 525 219, entitled "*GLP-1 and methods for treating diabetes*" could be maintained in amended form.

II. The opposition division considered a main request and five auxiliary requests. It did not admit auxiliary request 4 into the proceedings and held that the patent as amended according to auxiliary request 5 and the invention to which it related met the requirements of the EPC.

III. Claim 1 of auxiliary request 5 read:

"1. Use of at least one GLP-1 agonist having GLP-1 effect for the manufacture of a medicament for use in a method of preventing or treating diabetes in a mammal, wherein the method comprises the steps of (a) administering a therapeutically effective amount of the GLP-1 agonist at least once daily then (b) stopping administration of the GLP-1 agonist or reducing administration of the GLP-1 agonist below about the therapeutically effective amount for a time conducive to producing a drug holiday, wherein the drug holiday is further defined as a time interval between a first end-point following the stopping or reduction in administering the GLP-1 agonist in step (b) and a second end-point after which administration of a therapeutically effective amount of the GLP-1 agonist at least once daily is resumed, wherein the drug holiday is from three to four weeks, and wherein steps

(a) and (b) are repeated to provide a therapeutic regimen which includes two or more drug holidays".

Claim 2 was a further independent claim and claims 3 to 15 were dependent on claims 1 and 2.

IV. With the statement of grounds of appeal, appellant I filed an auxiliary request A and with the reply to the statements of grounds of appeal of appellants II and III, an auxiliary request E.

V. Claim 1 of auxiliary request A read:

"1. Use of at least one GLP-1 agonist having GLP-1 effect for the manufacture of a medicament for use in a method of preventing or treating diabetes in a mammal, wherein the method comprises the steps of (a) administering a therapeutically effective amount of the GLP-1 agonist then (b) stopping administration of the GLP-1 agonist or reducing administration of the GLP-1 agonist below about the therapeutically effective amount for a time conducive to producing a drug holiday, wherein the drug holiday is further defined as a time interval between a first end-point following the stopping or reduction in administering the GLP-1 agonist in step (b) and a second end-point after which administration of a therapeutically effective amount of the GLP-1 agonist is resumed,
wherein steps (a) and (b) are repeated to provide a therapeutic regimen which includes two or more drug holidays
and wherein each drug holiday is from three to twenty five weeks".

Claim 1 of auxiliary request E read:

"1. Use of at least one GLP-1 agonist having GLP-1 effect for the manufacture of a medicament for use in a method of preventing or treating diabetes in a mammal, wherein the method comprises the steps of (a) administering a therapeutically effective amount of the GLP-1 agonist at least once daily then (b) stopping administration of the GLP-1 agonist or reducing administration of the GLP-1 agonist below about the therapeutically effective amount for a time conducive to producing a drug holiday, wherein the drug holiday is further defined as a time interval between a first end-point following the stopping or reduction in administering the GLP-1 agonist in step (b) and a second end-point after which administration of a therapeutically effective amount of the GLP-1 agonist at least once daily is resumed,
wherein steps (a) and (b) are repeated to provide a therapeutic regimen which includes two or more drug holidays,
and wherein each drug holiday is from three to four weeks".

VI. In a communication pursuant to Article 15(1) RPBA, the board set out its preliminary appreciation of substantive and legal matters concerning the appeal.

VII. Appellants II and III replied to this communication with letters in which they informed the board that they would not attend the oral proceedings.

VIII. Oral proceedings before the board were held in the absence of appellants II and III. At the end of the proceedings, the Chairman announced the decision of the board.

IX. Appellant I requested that the decision under appeal be set aside and the patent be maintained on the basis of the claims of auxiliary request A, or alternatively, on the basis of the claims of auxiliary request E, or further alternatively, that the appeals of appellants II and III be dismissed. No other requests were maintained.

X. Appellants II and III requested in writing that the decision under appeal be set aside and the patent be revoked and that auxiliary request A not be admitted into the proceedings.

XI. The following documents are cited in this decision:

D1: Greig *et al.*, Diabetologia (1999), 42, 45-50

D2: Xu *et al.*, Diabetes (1999), 48, 2270-2276

D3: WO 00/09666

D7: Tourrel *et al.*, Diabetes (2002), 51(5), 1443-1452

D8: Wang *et al.*, Diabetologia (2002), 45, 1263-1273

D9: Fineman *et al.*, Diabetes (2002), 51, (Supplement 2), Abstract 343-OR

D10: Hui *et al.*, Eur. J. Endocrinology (2002), 146, 863-869

D12: WO 99/43708

D16: US 6 191 102

D18: Holst, Curr. Med. Chem. (1999), 6, 1005-1017

D24: Petersen *et al.*, Diabetologia (2002), 45, (Suppl. 1), A147, Abstract no. 447

D25: Petersen *et al.*, Diabetologia (2002), Poster presentation

D26: Thorkildsen *et al.*, Nedegaard Symposium (2002), Abstract

D27: Thorkildsen *et al.*, Nedegaard Symposium (2002), Poster Presentation

D38: Prescribing information for Victoza (liraglutide) submitted with appellant I's letter of 13 August 2012

XII. Appellant I's arguments relevant to the decision are summarised as follows:

Admission into the appeal proceedings - Article 12(4) RPBA

Auxiliary request A

Auxiliary request A, filed with the statement of grounds of appeal corresponded to auxiliary request 4, filed before the opposition division and in respect of which the opposition division had wrongly exercised its discretion in not admitting it into the proceedings.

Claim 1 was amended to specify the length of the "*drug holiday*" as being from three to twenty five weeks which differentiated the claimed subject-matter from conventional daily administration of the drug. This amendment took the opposition division's views on novelty, which had emerged during the oral proceedings

before it, into account. In such circumstances, amendments to the claims to address such issues were allowable.

In the present case, the subject-matter of the amendment, i.e. the time period of three to twenty-five weeks, was contained in claim 6 as granted, which the opponents should have been prepared to discuss (see Guidelines for Examination, E-IV, 2.2). Moreover, the auxiliary request met the requirement of "*clear allowability*" set out in the Guidelines (see Guidelines, E-IV 2.1).

Auxiliary request E

The claims of this request were essentially the same as auxiliary request 5 considered by the opposition division, any differences being of a purely organisational nature. Thus auxiliary request E should be admitted into the proceedings.

Inventive step (Article 56 EPC)

Auxiliary request 5 - claim 1

Each of documents document D3 and documents D24 to D27 disclosed the daily administration of a GLP-1 agonist for the treatment of diabetes and could serve to represent the closest prior art. Furthermore, all of these documents disclosed that GLP-1 and its agonists exhibited a so-called sustained effect, in other words they disclosed that the beneficial effects of the drug on insulin production and thus in control of blood sugar levels, continued once administration of the drug had ended.

In view of the benefits of a "*drug holiday*" regimen over said daily administration in avoiding adverse side effects (see the patent in suit, paragraphs [0014] to [0017] and [0022]), the objective technical problem was the provision of an improved therapeutic regimen for the treatment of diabetes.

The skilled person seeking an improved therapeutic regimen for treating diabetes and starting from the known daily administration regimen of a GLP-1 agonist (see e.g. document D3), would not have realised the significance of the sustained effects of GLP-1 and its agonists in terms of avoiding side effects. A "*drug holiday*" regimen had not been employed for the treatment of diabetes at all at the relevant date of the patent in suit, which reflected the fact that such a regimen went against the prevailing clinical practice of daily administration. Thus, the skilled person would not have implemented a "*drug holiday*" regimen as claimed as a solution to the technical problem.

Although documents D24 to D27 disclosed some of the same data as the patent in suit, showing a sustained effect for a GLP-1 agonist, these documents would not have led the skilled person to make a connection between said sustained effect and the dosing regimen.

Seeking to improve the existing therapy of diabetes by daily administration of a GLP-1 agonist, the skilled person, aware of the teaching of document D16, which taught that the breakdown and clearance rate of GLP-1 compounds were important problems, would have concentrated on addressing these problems.
Document D7 disclosed that the sustained effect of administration of GLP-1 or Exendin-4 in the prediabetic period rendered these compounds invaluable agents for

the prevention of type 2 diabetes. This showed that the skilled person knowing of the sustained effect of GLP-1 agonists would not have automatically arrived at the claimed subject-matter.

XIII. Appellant II and appellant III's arguments relevant to the decision are summarised as follows:

Admission into the appeal proceedings - Article 12(4) RPBA

Auxiliary request A

This claim request had not been presented during the opposition proceedings, even though all of the objections facing the proprietor had been raised in the notices of opposition. There was no justification for filing the request only at the appeal stage.

Inventive step (Article 56 EPC)

Auxiliary request 5 - claim 1

It was known from documents D1, D2, D3, D7, D10 and D24 to D27, for example, that the daily administration of GLP-1 and its agonists was a therapy for diabetes that allowed a patient to provide themselves with a useful amount of endogenous insulin, the beneficial effects lasting beyond the end of the administration of the drug. Document D3 (see Example 3), for instance reported that after administrating Exendin-4 to rats once a day for 5 days, new insulin producing cells outside the islet of Langerhans were observed in a location where such cells were not expected. Insulin production persisted for at least two weeks after stopping the administration of Exendin-4.

Documents D24 to D27 related to the daily administration of a GLP-1 agonist in the treatment of diabetes and contained the same data on the persistent effect of a GLP-1 agonist on control of blood glucose levels as the patent in suit. Any of these documents could therefore represent the closest prior art for the invention of claim 1. Regardless of exactly which document was chosen, the subject-matter of claim 1 differed in that it related to a regimen for the treatment of diabetes using a GLP-1 agonist including a break in the once-daily administration of GLP-1 agonist thereby producing a "*drug holiday*" of 3 to 4 weeks in a treatment regimen for diabetes.

The patent in suit contained lacked evidence that the claimed regimen had been put into practice, let alone that it was improved compared to the known daily administration regimen, especially in terms of better control of blood glucose levels. In view of this, the problem to be solved was the provision of an alternative method for the treatment of diabetes.

Seeking a solution to this problem, starting from a document disclosing the treatment of diabetes by once daily administration of a GLP-1 agonist and having knowledge of the sustained effect of GLP-1 agonists, the skilled person would have determined how long the effect lasted by routine monitoring of the blood glucose levels in the patient and would thus have known when to resume drug administration. It was therefore obvious to the skilled person that the claimed subject-matter, including a "*drug holiday*", would solve the above problem. The claimed subject-matter lacked inventive step.

Reasons for the Decision

1. Oral proceedings before the board were held in the absence of appellants II and III, in accordance with Rule 115(2) EPC and Article 15(3) RPBA. Accordingly, these appellants are treated as relying on their written case.

Admission into the appeal proceedings - Article 114(2) EPC

2. The board has the power to hold inadmissible requests which could have been presented or were not admitted in the first-instance proceedings (Article 12(4) RPBA).

Auxiliary request A

3. According to established case law, a board should only overrule the way in which a department of first instance exercised its discretion under Article 114(2) EPC, if the board concludes it has done so according to the wrong principles, or without taking into account the right principles, or in an unreasonable way (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition, IV.E.3.6).

4. The opposition division held that claims 1 and 2 of auxiliary request 4, filed during oral proceedings, included a time period for the "*drug holiday*" which changed the focus of the technical debate in comparison with the preceding claim requests. The opposition division also considered that the opponents had not had sufficient opportunity to prepare for this change (see decision under appeal, item 14 *ff*).

5. In taking the decision not to admit the request, the opposition division balanced the interests of the

patentee to react to its views on the novelty of the preceding request, with those of the opponents to react to amended subject-matter and took into account the stage of the proceedings at which the requests were submitted, their content and the impact their admission would have had on the proceedings.

6. There is nothing on file that would lead the board to conclude that the opposition division did not exercise its discretion in accordance with the right principles or in a reasonable way. Accordingly, auxiliary request A is not considered in the appeal proceedings.

Auxiliary request E

7. Auxiliary request E was filed with appellant I's reply to the statements of grounds of appeal of appellants II and II. Appellant I considered that "*Auxiliary Request E [...] corresponds to fifth auxiliary claim request maintained by OD and requests the discretion of the Board in admitting this request into the proceedings*".

8. The board notes that claim 1 is not identical with claim 1 of auxiliary request 5 (see Sections III. and V.). Appellant I has not, either in writing or at the oral proceedings, provided an explanation for the amendments made in auxiliary request E *vis-à-vis* auxiliary request 5, or given a reason why the request could not have been presented earlier.

9. In the absence of any persuasive justification for the amendments made, the board sees no reason to admit auxiliary request E into the proceedings (Article 12(4) RPBA).

Auxiliary request 5

Inventive step (Article 56 EPC) - claim 1

10. Claim 1 is for the therapeutic application of "*at least one GLP-1 agonist having GLP-1 effect*" in "*the prevention or treatment of diabetes in a mammal*", including the feature of the administering a GLP-1 agonist in a regimen including two or more effective breaks in the administration, termed "*drug holidays*".

Closest prior art

11. Document D3 relates to methods of treating patients having Type 1 diabetes by daily administration of GLP-1 or Exendin-4. It discloses "[T]*the administration of GLP-1, Exendin-4, or related peptides increases the number of insulin-producing cells, an effect that is desirable in the treatment of diabetes mellitus*" (see paragraph bridging pages 13 and 14) and that administration of Exendin-4 converts non-insulin producing cells to a population of insulin producing cells, which, after 5 days "*were proliferating cells in the islet. In addition, there were proliferating cells lining the ducts and, more surprisingly, in the acinar tissue, an area generally considered to be devoid of stem cells. Also surprisingly, a number of insulin positive cells were found outside the islets among the acinar tissue, where insulin positive cells are not expected.*" (see page 40ff, Example 3). Exendin-4 has a much longer half-life than GLP-1, which allows its administration as a daily bolus injection, rather than as continuous infusion. It is disclosed that *"After two injections, insulin producing cells outside the islet are observed. The maximal effect is achieved by seven days. As with GLP-1, the effect persists for at least*

two weeks, and probably permanently, even after contact with the Exendin-4 is discontinued" (*ibid.*).

12. Thus, both document D3 and the subject-matter of claim 1 concern the daily administration of GLP-1 agonists for treating diabetes in a mammal. Moreover, both relate to an administration regimen including a period of treatment followed by the stopping of that treatment and to a sustained effect of a GLP-1 agonist on insulin levels, i.e. an effect on insulin production that continues after the administration of the drug has stopped. Document D3 is therefore considered by the board as suitable for representing the closest prior art.

13. Appellants II and III also suggested that also the disclosure in any of documents D2, D7, D10 and D24 to D28 could serve to represent the closest prior art. Indeed, documents D24 to D28 included some of the same experimental data as the patent in suit and all documents disclosed the sustained effect of GLP-1 agonists on insulin production and thus on control of blood glucose. In this respect, the board recognises that the above mentioned documents relate to GLP-1 agonists and their use in treating diabetes in a mammal, as to sustained effects of the GLP-1 agonists in terms of control of blood glucose levels. It notes, however, that only document D3 explicitly discloses stopping the administration of the GLP-1 agonist, Exendin-4 and mentions that its effects extended beyond said stopping (see page 40 ff, Example 3 and claim 37). Document D3 thus shares an additional technical feature (the stopping of the administration) with the claimed subject-matter.

14. Thus document D3 relates to treatment of a diabetic mammal with a therapeutically effective amount of GLP-1 agonist at least once daily for a period of time and then stopping this administration. Claim 1 on the other hand explicitly refers to the stopping of such treatment followed by its resumption of treatment after 3 to 4 weeks followed by a second and possibly further "*drug holidays*".

15. The patent in suit states that the effect of the "*drug holiday*" is to "*provide mammals and especially human patients with much sought after relief from invasive, sometimes painful, and often repetitive and expensive therapies and allow potentially serious side-effects and related complications often associated with such therapies to be reduced, delayed, or in some instances eliminated*" (see paragraph [0022] of the patent in suit). The technical effect of the above mentioned difference is therefore the avoidance of deleterious effects associated with the administration of the GLP-1 agonist.

The technical problem and its solution

16. In view of the above mentioned difference and the technical effect thereof, the objective technical problem can be formulated as the provision of a therapeutic regimen for the treatment of diabetes by administering a GLP-1 agonist with reduced negative effects in comparison to a daily administration regimen.

17. Although the patent discloses no experimental report of an administration regimen for a GLP-1 agonist implementing a drug holiday of any kind and thus provides no direct evidence that the problem is solved

by the claimed invention, the board considers it to be self-evident to the person skilled in the art that interrupting the administration of a therapeutically effective dose of a GLP-1 agonist for a period of time, as claimed, will bring the desired benefit of reduced negative effects caused by said GLP-1 agonist. Control of blood glucose level can be accepted as being achieved because of the documented sustained effect of GLP-1 agonists (*c.f.* the Examples 3 and 4 of the patent in suit and the disclosures of documents D2, D3, D7, D10 and D24 to D28) and of the resumption of agonist therapy as claimed, once the sustained effect has worn off.

Obviousness

18. It has to be established whether or not it was obvious for the skilled person, starting from the disclosure of document D3, to implement a "*drug holiday*" regimen as claimed, i.e. to resume administration of the GLP-1 agonist three to four weeks after stopping it and to repeat this regimen as often as necessary, as a solution to the above formulated technical problem.

19. The need to resume daily administration of the GLP-1 agonist once its sustained effect on insulin production wears off, stems from the need to maintain control of the blood glucose levels in the patient. Indeed, this was the very reason for the diabetic patient's initial treatment with the GLP-1 agonist. Resumption of daily administration of the drug was the simplest effective treatment option for controlling blood glucose levels in a diabetic patent, known *inter alia* from any of documents D2, D3, D7, D10 and D24 to D28 and is therefore judged by the board not to have required inventive skill from the skilled person.

20. That a "*drug holiday*" dosing regimen could be repeated once or more than once, in the course of the prevention or treatment of diabetes in a patient, would have been obvious to the skilled person for the same reasons that a single "*drug holiday*" was obvious, stemming from goals of avoiding side effects and maintaining control of blood glucose levels in the patient.

21. No case has been made by appellant I that a surprising or unexpected technical effect is associated with the particular length of the "*drug holiday*", as claimed. In the board's view, the three to four week duration of the holiday mentioned in the claim must therefore be regarded as an arbitrary choice, which therefore does not affect the definition of the technical problem. The inclusion of the three to four week period in the subject-matter of claim 1 without a particular technical effect is considered to constitute an obvious measure.

22. In view of the above considerations, the subject-matter of claim 1 of auxiliary request 5 is regarded as obvious in the light of the disclosure of document D3, on its own or in combination with any of documents D2, D7, D10 and D24 to D28.

23. Document D16 relates to the use of GLP-1, analogs and derivatives of GLP-1, in methods and compositions, that promote weight-loss (see column 1, lines 10 to 13). In cases where administration is intermittent, it was recommended to adjust the dose of the GLP-1 or analog thereof per administration to take into account the interval between doses, and the bioavailability of the administered compound (see paragraph bridging columns 14 and 15).

24. Appellant I argued that the skilled person reading document D16 was led away from the claimed invention because of the disclosure that the dose of GLP-1 or analog thereof should be adjusted to compensate in cases where the administration was intermittent.

25. The board however, notes that the disclosure referred to in document D16 was made in the context of the dosing GLP-1 and its analogs for treatment of obesity (see document D16, title) and not of diabetes. The board judges that the skilled person would not have automatically transferred a dosage regimen for treating obesity to one for the treatment of diabetes. Thus the argument that the disclosure of document D16 taught the skilled person away from the invention has not been substantiated and must fail.

26. Document D7 disclosed the therapeutic application for Exendin-4 for the prevention of human type 2 diabetes. Appellant I argued this disclosure demonstrated that the skilled person, at the relevant date of the patent, had choices in how to use the knowledge of the sustained effect of GLP-1 agonists. The claimed invention was therefore not the only inevitable result of this knowledge.

27. For the board, the existence of additional therapeutic applications of GLP-1 agonists does not however affect the outcome of the assessment of obviousness done according the problem and solution approach set out above. In fact, the disclosure of document D7 may have strengthened the skilled person's notions concerning the ß-cell replenishing effect of GLP-1 agonist therapy, leading to increased confidence that implementing a "*drug holiday*" in the administration regimen of such agonists in the treatment of diabetes,

would allow control of blood glucose levels to be maintained.

28. In view of the above considerations, the subject-matter of claim 1 of auxiliary request 5 is held to have been obvious to the skilled person having regard to the state of the art. The sole pending claim request does not meet the requirements of Article 56 EPC and is not allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

P. Cremona B. Claes

Decision electronically authenticated