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D E C I S I O N
of 5 July 2004

Case Number: T 0940/02 - 3.3.4

Application Number: 93907820.0

Publication Number: 0631505

IPC: A61K 38/26

Language of the proceedings: EN

Title of invention:

Use of a peptide

Patentees:

NOVO NORDISK A/S, et al

Opponent:

Eli Lilly and Company

Headword:

Use of a peptide/NOVO NORDISK A/S

Relevant legal provisions:

EPC Art. 123(3), 83, 56

Keyword:

"Main Request - Auxiliary Requests 1 and 2: Inventive step
(no) "

"Auxiliary Request 3: Added subject-matter (no) - Sufficiency
of disclosure (yes) - Inventive step (yes) "

Decisions cited:

T 0923/92

Catchword:

-



Case Number: T 0940/02 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 5 July 2004

Appellants: NOVO NORDISK A/S et al
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 9 August 2002
revoking European patent No. 0631505 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
R. Moufang

Summary of Facts and Submissions

I. The appeal is against the decision of the opposition division revoking European patent No. 0 631 505 (application No. 93907820.0 published as WO 93/18786), which had been opposed by the respondent (opponent) on the grounds of Articles 100(a) (Articles 54 and 56) and 100(b) EPC. Independent claim 1 as granted read as follows:

"1. Use of an effective amount of GLP-1(7-37), GLP-1(7-36) amide, or a pharmaceutically acceptable peptide containing a fragment of the GLP-1(7-37) sequence, or an analogue or a functional derivative of such a peptide for the preparation of a medicament for use in the treatment of type 2 diabetes in a regimen which additionally comprises treatment with an oral hypoglycaemic agent which is a blocker of the ATP-dependent potassium channel on β -cells."

Claims 2 to 5 related to specific embodiments of the use of claim 1.

II. The reasons given for the revocation were that claim 1 of the main request and auxiliary request 1 then on file lacked novelty, while claim 1 of auxiliary requests 2 and 3 did not involve an inventive step.

III. With the Grounds of Appeal the appellants filed a new **Main Request**, of which claim 1 read as follows:

"1. Use of an effective amount of an insulinotropic agent selected from GLP-1(7-37), GLP-1(7-36) amide, or an analogue of such a peptide for the preparation of a

medicament for use in the treatment of type 2 diabetes in a regimen which additionally comprises treatment with an oral hypoglycaemic agent which is a blocker of the ATP-dependent potassium channel on β -cells."

IV. Oral proceedings were held on 5 July 2004, during which the appellants filed New Auxiliary Requests 1 to 4.

Claim 1 of **Auxiliary Request 1** read as follows:

"1. Use of an effective amount of an insulinotropic agent selected from GLP-1(7-37), GLP-1(7-36) amide, or an analogue of such a peptide for the preparation of a medicament for use in the treatment of type 2 diabetes in a regimen which additionally comprises treatment with an oral hypoglycaemic agent which is a sulfonylurea which is a blocker of the ATP-dependent potassium channel on β -cells

(i) characterised in that the use in the treatment of type 2 diabetes is in a type 2 diabetic patient in whom sulphonylurea administration alone does not suffice to normalise blood sugar levels

or

(ii) characterised in that the use in the treatment of type 2 diabetes is in a type 2 diabetic patient with secondary failure to sulphonylurea treatment in whom sulphonylurea administration alone no longer normalises blood sugar levels."

Claim 1 of **Auxiliary Request 2** read as follows:

"1. Use of an effective amount of an insulinotropic agent selected from GLP-1(7-37), GLP-1(7-36) amide, or an analogue of such a peptide wherein at least one of the amino acid residues of GLP-1(7-37) or GLP-1(7-36) amide has been exchanged for another amino acid residue and/or wherein amino acid residues have been added at, or deleted from, the N-terminal and/or the C terminal end of the peptide GLP-1(7-37) or GLP-1(7-36) amide wherein the total number of additions, deletions and/or amino acid residues exchanged does not exceed five for the preparation of a medicament for use in the treatment of type 2 diabetes in a regimen which additionally comprises treatment with an oral hypoglycaemic agent which is a sulfonylurea which is a blocker of the ATP-dependent potassium channel on β -cells

(i) characterised in that the use in the treatment of type 2 diabetes is in a type 2 diabetic patient in whom sulphonylurea administration alone does not suffice to normalise blood sugar levels

or

(ii) characterised in that the use in the treatment of type 2 diabetes is in a type 2 diabetic patient with secondary failure to sulphonylurea treatment in whom sulphonylurea administration alone no longer normalises blood sugar levels."

Auxiliary Request 3 consisted of two claims:

"1. Use of an effective amount of GLP-1(7-37) or GLP-1(7-36) amide for the preparation of a medicament for use in the treatment of type 2 diabetes in a regimen which additionally comprises treatment with an oral hypoglycaemic agent which is a sulfonylurea which is a blocker of the ATP-dependent potassium channel on β -cells characterised in that the use in the treatment of type 2 diabetes is in a type 2 diabetic patient with secondary failure to sulphonylurea treatment.

2. Use according to Claim 1 when the oral hypoglycaemic agent is glibenclamide or glipizide."

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

(D1) Groop L. et al., Acta Endocrinologica, Vol. 106, pages 97-101 (1984);

(D2) Del Prato S., Am. J. Medicine, Vol. 90, Suppl. 6A, pages 77S-82S (24 June 1991);

(D3) Parker J.C. et al, Diabetes, Vol. 40, Suppl. 1, page 237A (1991);

(D3A) Poster No. 947 by Parker J.C. et al. and selected pages from the Official Program Guide for the 14th International Diabetes Federation Conference (23 to 28 June 1991), Convention Center, Washington DC;

- (D3B) Selected pages from the Official Program Guide for the 14th International Diabetes Federation Conference (23 to 28 June 1991), Convention Center, Washington DC;
- (D7) Nathan D.M. et al, Diabetes Care, Vol. 15, No. 2, pages 270-276 (February 1992);
- (D8) Gutniak M.K. et al., Diabetes Care, Vol. 19, No. 8, pages 857-863 (August 1996);
- (D9) Declaration of Dr. J. Sturis dated April 2002 (appellants);
- (D11) Flatt P.R. et al., Diabetologica, Vol. 43, Suppl. 1, page A30, Abstract No. 119 (2000);
- (D12) McClenaghan N.H. et al., abstract submitted for presentation at the Meeting of the European Association of the Study of Diabetes of September 2002;
- (D13) Hargrove D.M. et al., Metabolism, Vol. 45, No. 3, pages 404-409 (March 1996);
- (D14) Declaration of Prof. P.R. Flatt dated 29 November 2002 (appellants);
- (D15) Declaration of Prof. K. Buschard dated 3 December 2002 (appellants);
- (D16) Second Declaration of Dr. J. Sturis (appellants);

- (D17) Alberti K.G.M.M. et al., Diabetic Medicine,
Vol. 5, pages 275-281 (1988);
- (D18) Declaration of Prof. M. Væth dated 1 June 2004
(appellants);
- (D19) Declaration of Dr. S.D. Beattie dated 1 May 2003
(respondent);
- (D20) Declaration of Dr. J.M. Beals dated 18 April 2002
(respondent);
- (D21) Declaration of Prof. R.J. Carroll dated
13 September 2000 (respondent).

VI. The submissions by the appellants (patentees), insofar as they are relevant to the present decision, can be summarized as follows:

Main Request

Article 123(3) EPC

- The wording "or an analogue ...of such a peptide" in granted claim 1 related not only to "a pharmaceutically acceptable peptide" but also to the peptides GLP-1(7-37) and GLP-1(7-36)amide, wherein the acronym "GLP" meant glucagon-like peptide, especially if the claim was interpreted in the light of paragraph [0026] of the description. Therefore, the analogues of GLP-1(7-37) and GLP-1(7-36)amide were already covered by granted claim 1.

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 and the insulinotropic activity could easily be tested by the skilled person. Moreover, no substantiation by way of verifiable facts had been provided by the respondent against the claimed generalisation.

- Once the present inventors demonstrated a synergistic effect in vivo between GLP-1(7-36)amide and glibenclamide, it was reasonable to expect that such an effect would also be obtained by combinations of other members of the two classes (GLP-1 analogues and sulfonylureas).

- The fact that Dr. Beals, a respondent's expert (see Declaration (D20)) was in a position to find active analogues, supported the appellants' case. Appellants' test report (D9) (see Fig. 1B) further showed that these analogues acted synergistically with glipizide.

Article 56 EPC

- Unlike document (D3) dealing with in vitro investigations and which the respondent considered as closest prior art, document (D7) represented the closest prior art document for the determination of inventive step, as it was specifically concerned with the therapeutic in vivo potential of GLP-1 compounds in type 2

diabetic patients. The problem to be solved was the provision of further therapies for these patients. The solution proposed was the combination referred to in claim 1.

- Even if, starting from document (D7), a skilled person came across document (D3) when considering further treatments for type 2 diabetes, he/she would not be motivated to use a combination therapy on the following grounds:
 - Before the priority date of the patent in suit, the prevailing wisdom in the field of the treatment of type 2 diabetes (see document (D17)) was against the use of a combination therapy because, inter alia, treatment with sulfonylurea carried a considerable risk of hypoglycaemia (see ibidem, page 277, right hand column and document (D3B)). For these reasons, document (D7) (see page 275) presented GLP-1(7-37) as a hypoglycaemia-free **alternative** to the use of sulfonylureas. This trend to use GLP-1 peptides alone was confirmed by later document (D13).
 - The conclusion of an additive effect in vitro was scientifically unsound since there were scientific flaws in the design of the experiments conducted according to document (D3). In particular, the conditions (perifusion versus static administration) under which the first and third experiments had been carried out were completely different. But it was already well-known at the time the abstract was published that marked differences in insulin

secretory response existed between different in vitro systems. Therefore, it was not scientifically possible to draw any conclusions about what effects, if any, the combination of GLP-1 and glibenclamide might have on insulin secretion from cells in vitro, let alone in vivo (see Declarations (D14) and (D15)).

Synergy

- The existence of a synergistic effect would constitute a further inventive step from the prior art, but a single inventive step (not a "staircase") was all that was required to comply with Article 56 EPC. In any case, a synergistic effect had been demonstrated.

Auxiliary Requests 1 and 2

Article 123(2) EPC

- There was a basis on page 2, second paragraph of the application as filed for the wording (i) or (ii) in claim 1 of both requests.

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 and the insulinotropic activity could easily be tested by the skilled person.

Article 56 EPC

The patients referred to in claim 1 of these requests were those wherein sulfonylurea administration alone did not suffice to normalise blood sugar levels or who were suffering from secondary failure to sulfonylurea treatment, wherein sulfonylurea administration alone no longer normalised blood sugar levels. The authors of document (D3) did not use this model for their studies. The skilled person would have thus not used the combination described in this document to treat these patients with a reasonable expectation of success. It was thus unexpected that such patients could still be treated with a combination of GLP-1(7-37) or GLP-1(7-36)amide and a sulfonylurea, owing to the surprising synergistic effect arising in such a combination.

Auxiliary Request 3

Article 83 EPC

- Claim 1 of this request was restricted to a medical use involving a combination of GLP-1(7-37) or GLP-1(7-36)amide with a sulfonylurea. The number of possible combinations to be tested was thus limited and the insulinotropic activity could easily be tested by the skilled person.

Article 56 EPC

- The patients referred to in claim 1 of this requests were suffering from a secondary failure to sulfonylureas, ie whose treatment with

sulfonylureas was discontinued and switched to insulin. The skilled person would not expect any therapeutic advantage by administering to these patients a further sulfonylurea or another agent stimulating the β -cell function, or with a combination of these agents. It was thus unexpected that such patients could still be treated with a combination of GLP-1(7-37) or GLP-1(7-36)amide and a sulfonylurea, owing to the surprising synergistic effect arising in such a combination.

- Post-published documents (D8) and (D11) and test reports (D9) and (D16) clearly demonstrated that a synergistic effect was obtained with the claimed combination. Figure 2 of test report (D9) by Dr. Sturis showed a greater than additive effect for different GLP-1 analogues and glipizide.
- Dr. Sturis obtained further confirmatory data in a second series of experiments (see document (D16)), wherein four treatment groups were included (controls, glipizide only, GLP-1 only, or a combination of glipizide with GLP-1, the latter being administered concomitantly to pancreas tissue). The figure under "Results" showed a marked and statistically significant synergistic effect on insulin secretion when a combination of glipizide and GLP-1 was used.

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

Main Request

Article 123(3) EPC

- Granted claim 1 only covered the use of analogues of fragments of GLP-1(7-37) and GLP-1(7-36)amide for the preparation of a medicament. However, the scope of claim 1 of this request had been extended to also cover analogues of GLP-1(7-37) and GLP-1(7-36)amide (c.f. the wording "or an analogue of such a peptide").

Article 83 EPC

- Claim 1 did not impose any limit on the nature or number of amino acid substitutions, additions or deletions in the "analogue". Declaration (D20) showed that one or two amino acid changes could have dramatic effects on the activity of the GLP-1 analogues.
- Moreover, even if synergy between GLP-1(7-37) and glipizide was accepted, such a synergistic effect had not been shown to extend over the full scope of claim 1. In conclusion, the patent imposed an undue burden on the skilled person to identify these insulinotropic "analogues" and synergistic combinations from the myriad possibilities.
- The activity of GLP-1 analogues and sulfonylureas being glucose-dependent, the patent in suit did not provide any information relating to the glucose levels at which the synergistic effect could be obtained in vivo.

- Claim 1 also failed to specify the route of administration of the GLP-1 related peptides. According to the description, the GLP-1 related peptide could be administered in any of a variety of ways, including injection, oral administration (e.g. tablets) and nasal administration (page 4, lines 30 to 36). However, the patent in suit did not teach the reader how to obtain a synergistic response when GLP-1(7-37) was administered by any of these alternative routes.

Article 56

- At the priority date of the patent in suit it was common general knowledge that sulfonylureas such as glibenclamide were used in the treatment of type 2 diabetes and that further compounds considered as possible insulinotropic agents for the treatment of type 2 diabetics were GLP-1(7-37) and GLP-1(7-36)amide. There was thus no invention in merely combining two known pharmaceutically active agents for their known purpose.
- Document (D3) was concerned with experiments regarding the mechanisms of action of GLP-1(7-37) and glibenclamide in rat pancreatic islets and HIT cells. The document reported that GLP-1(7-37) (10 nM), when added to islets incubated with 8 mM glucose plus a maximally effective dose of glibenclamide caused a further increase in insulin secretion. Accordingly, the skilled person was clearly taught that a combination of GLP-1(7-37) and glibenclamide provided greater insulin release than glibenclamide alone.

- A further relevant fact disclosed by document (D3) was that maximally effective doses of GLP-1(7-37) and glibenclamide on their own produce approximately the same amount of insulin release. However, as already discussed above, it was part of the common general knowledge of those skilled in the treatment of type 2 diabetes at the priority date of the patent in suit that a maximally effective dose of glibenclamide was not sufficient for a large number of patients. There was thus a positive incentive to use GLP-1(7-37) in combination with glibenclamide at the priority date, in the expectation of providing improved treatment.
- Where, as here, the prior art provided a clear incentive to follow a particular route, in the expectation of an advantage, a "one-way street" situation existed. Therefore the claims of the opposed patent lacked inventive step, irrespective of any synergy which might be observed when GLP-1(7-37) and glibenclamide were used together.
- Post-published document (D13) could not reflect the thinking of those skilled in the art at the priority date of the patent in suit.
- Administration of insulin also carried a risk of hypoglycaemia. Nevertheless, the risk was not such as to dissuade diabetics from using insulin, either alone or in conjunction with sulfonylureas (see e.g. documents (D1) and (D2)). The prejudice

against using a sulfonylurea together with a GLP-1(7-37) had thus not been proved.

Auxiliary Requests 1 and 2

Article 83 EPC

- The patent imposed an undue burden on the skilled person to identify all the synergistic combinations covered by claim 1 and failed to teach the skilled person how to obtain a synergistic response when the combination was administered by alternative routes.

Article 56 EPC

- According to paragraph [003] of the patent in suit, the majority of patients suffering from diabetes type 2 were still treated with agents that stimulated the β -cell function, ie the latters were not completely unreactive to the stimulating action of sulfonylureas, i.e. sulfonylureas still sensitised β -cells, although normal blood sugar levels were not achieved. There was thus still an incentive to use sulfonylureas, possibly supplemented with GLP-1 as suggested by document (D3).

Auxiliary Request 3

Article 83 EPC

- The patent imposed an undue burden on the skilled person to identify all the synergistic combinations covered by claim 1 and failed to teach the skilled person how to obtain a

synergistic response when the combination was administered by alternative routes.

Article 56 EPC

- Synergy between GLP-1(7-37) and sulfonylureas was not satisfactorily demonstrated.
- There were inconsistencies between the tests of document (D9) (7.5 nM glucose and 30 pM GLP-1) and those of document (D16) (8 nM glucose, 56 pM GLP-1).
- As for document (D16), it merely showed a chart with error bars, and an asserted probability <0.05 (according to a t-test) for the absence of synergy. However, the reliance on a t-test to argue synergy required that the data had to be consistent with a normal distribution. This was not the case as the bar chart in document (D16) showed a variability (ie standard deviations) which was a function of the mean response (see declaration (D19), which also showed that documents (D9) and (D11) failed to provide a sound statistical basis for synergism).
- The most that document (D16) demonstrated was synergy in vitro between GLP-1 and glipizide without any implication regarding a possible in vivo effect.

VIII. The appellants (patentees) requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 5 of the main

request filed with the grounds of appeal or of claims 1 to 3 of auxiliary request 1 or 2 or of claims 1 and 2 of auxiliary request 3 or of the sole claim of auxiliary request 4, all submitted during oral proceedings.

The respondent (opponent) requested that the appeal be dismissed.

Reasons for the decision

1. The appeal is admissible.

Main Request

Article 123(3) EPC

2. The respondent argues that granted claim 1 (c.f. "... GLP-1(7-37), GLP-1(7-36)amide or a pharmaceutically acceptable peptide containing a fragment of the GLP-1(7-37) sequence, or an analogue or a functional derivative of such a peptide...") only covered the use of analogues of fragments of GLP-1(7-37) and GLP-1(7-36)amide for the preparation of a medicament and that the scope of claim 1 of this request (c.f. the wording "...or an analogue of such a peptide...") has been extended to also cover analogues of GLP-1(7-37) and GLP-1(7-36)amide.
3. However, the wording "...or an analogue or a functional derivative of such a peptide..." in granted claim 1 relates not only to "...a pharmaceutically acceptable peptide containing a fragment of the GLP-1(7-37) sequence..." but also to the peptides GLP-1(7-37) and

GLP-1(7-36)amide, wherein the acronym "GLP" means glucagon-like peptide. Therefore, the analogues of GLP-1(7-37) and GLP-1(7-36)amide were already covered by granted claim 1. This interpretation is corroborated by paragraph [0026] of the description, giving the definition of the wording "analogues of GLP-1(7-37) and GLP-1(7-36)amide". In conclusion, the board sees no offence against the requirements of Article 123(3) EPC.

Article 83 EPC

4. The board sees the possible relevance of the objections raised by the respondent under this Article. However, in view of the board's negative conclusions on the fulfilment of the requirements of Article 56 EPC (see point 10 *infra*), the board finds it superfluous to deal with this issue. Detailed reasons for claims being regarded as allowable under Article 83 EPC will be given (see Auxiliary Request 3, point 21 *infra*).

Inventive step (Article 56 EPC)

Closest prior art

5. The appellants consider document (D7) as representing the closest prior art for the determination of inventive step. However, the board does not share this view and favours document (D3) for this purpose. This is because document (D3) relates to both components (GLP-1(7-37) and glibenclamide) of the binary combination referred to in claim 1, unlike document (D7), which discloses only one, (GLP-1(7-37)), of the two. The "monotherapy theory" is also not convincing (see point 12 *infra*).

The problem to be solved

6. The problem to be solved is the provision of a further therapy for diabetes type 2. The proposed solution is the combination of a GLP-1 peptide and an oral hypoglycaemic agent which is a blocker of the ATP-dependent potassium channel on β -cells. The examples in the patent in suit show that such a combination can be used successfully to treat type 2 diabetes patients.
7. The relevant question is whether it was obvious or not for the skilled person to arrive at the use of claim 1, characterized by the treatment of type 2 diabetes with the above combination.
8. Document (D3) is concerned with experiments regarding the mechanisms of action of GLP-1(7-37) and glibenclamide in rat pancreatic islets and HIT cells. It is stated in this abstract that: "...islets were perfused with ...a **maximally-effective dose** of GLP-1(7-37) (10 nM) or glibenclamide (10 μ M)..." and "GLP-1(7-37) (10 nM), when added to islets statically incubated with 8 mM glucose plus a **maximally effective dose** of glibenclamide (10 μ M), caused a further increase in insulin secretion (1.44 \pm 0.21 fmol/islet/min to 2.89 \pm 0.28 fmol/islet/min, P < 0.05" (emphasis by the board).
9. As highlighted above, the tests described in document (D3) were performed with maximally effective doses of GLP-1(7-37) (10 nM) and glibenclamide (10 μ M). This means that e.g. 10 μ M glibenclamide provided the highest insulin release that could be obtained when glibenclamide was used alone, i.e. adding a higher

concentration of this compound would not cause additional insulin secretion from the islets' β -cells. In spite of that, the authors of document (D3) found that adding GLP-1(7-37) (10 nM) to this 10 μ M glibenclamide "caused a further increase in insulin secretion" and concluded that a different mechanism of action underlay insulin release by GLP-1(7-37) and glibenclamide from the islets' β -cells.

10. In the board's judgement, there was thus an incentive at the priority date of the patent in suit to use GLP-1(7-37) in combination with glibenclamide, the latter being "an oral hypoglycaemic agent which is a blocker of the ATP-dependent potassium channel on β -cells" (see claim 1), since the skilled person was taught that a combination of GLP-1(7-37) and glibenclamide provided a greater insulin release than glibenclamide alone. The skilled reader of document (D3) would have appreciated that even an additive response would be clinically worthwhile, in view of the expectation of an **improved** treatment, irrespective of any synergy (see points 28 and 29 infra) which might be observed when GLP-1(7-37) and glibenclamide were used together. Therefore claim 1 of the main request lacks an inventive step and this request is refused.

11. To the several further arguments submitted to argue inventive step, the board observes the following:

Relying on documents (D17)) and (D3B), the appellants maintain that the considerable risk of hypoglycaemia arising from the presence of a sulfonylurea represented a strong prejudice against trying to use a combination of a sulfonylurea with GLP-1 peptides, all the more so

as document (D7) (see page 275) presented GLP-1(7-37) as a hypoglycaemia-free **alternative** to the use of sulfonylureas.

12. However, on page 275, r-h column of document (D7) it is stated that the administration of insulin also carries a risk of hypoglycaemia. Nevertheless, this risk was not such as to dissuade diabetics from using insulin either alone or in conjunction with sulfonylureas, as disclosed, for example in documents (D1) and (D2). A proper control of diabetes involves striking a balance between hypo- on the one hand and hyperglycaemia on the other. In conclusion, there is no convincing evidence before the board that in the present case a prejudice existed in the state of the art which would have diverted the skilled person away from the simultaneous administration of a sulfonylurea with a GLP-1 peptide.

13. It is further argued by the appellants that, owing to the scientific flaws (i) to (iii) below in the design of the experiments conducted according to document (D3), the skilled person could not draw any conclusions about what effects, additive or otherwise, the combination of GLP-1 and glibenclamide might have on insulin secretion from β -cells in vitro, let alone in vivo:
 - (i) The effect of GLP-1(7-37) on its own (ie, without glibenclamide) in the static incubation system has not been measured (see document (D14), section 11 and document (D15), section II(ii)).

 - (ii) GLP-1(7-37) and glibenclamide had been tested at less than maximal doses (see legend to Fig. 5 of document (D3A)).

(iii) In vitro tests cannot be extrapolated to the in vivo situation (see document (D15), section II(ii): "toxicity problems cannot be ruled out").

14. As for scientific flaw (i), Figure 5 of document (D3A), namely the "poster" presented to the public at the 14th International Diabetes Federation Conference (23 to 28 June 1991) and underlying later published abstract (D3) shows that the effect of GLP-1(7-37) on its own has also been measured by the authors of documents (D3) and (D3A).

As for flaw (ii), the wording "less than maximally" (see legend to Figure 5 of document (D3A)) rather relates to the glucose concentration, not to that of GLP-1(7-37) and glibenclamide, which have indeed been tested at their maximally effective doses of 10 nM and 10 μ M, respectively (see *ibidem*, Fig. 3a and 3b: "the maximum stimulation").

As regards deficiency (iii), it is true that the investigations on the combination GLP-1 peptide/sulfonylurea according to documents (D3) and (D3A) have been performed in vitro on islets. However, the single components were already known to the skilled person to be active and to lack toxicity in vivo on their own (for GLP-1(7-37): see document (D7); for sulfonylureas: see document (D17), page 277, r-h column). Neither did the appellants provide any evidence in support of the assertion that the in vivo effectiveness of the GLP-1 peptide could be reduced by the concurrent administration of a sulfonylurea, or

that simultaneous administration of the two components could bear some risk due to potential interactions between the two drugs. Therefore this appellants' argument is also not convincing.

15. None of the above appellants' arguments are thus susceptible to alter the view the board has come to (see point 10 supra) that document (D3) provided an incentive to use GLP-1(7-37) in combination with glibenclamide, the latter being an "oral hypoglycaemic agent which is a blocker of the ATP-dependent potassium channel on β -cells".

Auxiliary Requests 1 and 2

Article 123(2) EPC

16. Insert (i) "...the treatment of type 2 diabetes is in a type 2 diabetic patient in whom sulphonylurea administration alone does not suffice to normalise blood sugar levels" and insert (ii) "...the treatment of type 2 diabetes is in a type 2 diabetic patient with secondary failure to sulphonylurea treatment in whom sulphonylurea administration alone no longer normalises blood sugar levels" in claim 1 of both requests (see Section IV supra) find a basis on page 2, lines 8-18 and Example 2 (c.f. "patients with secondary failure to sulfonylureas") of the published application WO 93/18786 as filed.

Article 83 EPC

17. In view of the board's negative conclusions on the fulfilment of the requirements of Article 56 EPC (see

point 19 infra), the board will not deal with this issue.

Article 56 EPC

18. According to claim 1 of these requests the patient suffering from type 2 diabetes being treated may be, inter alia, "a type 2 diabetic patient in whom sulphonylurea administration alone does not suffice to normalise blood sugar levels". According to paragraph [003] of the patent in suit, the majority of patients suffering from diabetes type 2 (NIDDM) were still treated with agents that stimulated the β -cell function, the latter being not completely unreactive to the stimulating action of sulfonylureas, which still sensitised β -cells, although normal blood sugar levels were not achieved.

Closest prior art and problem to be solved

19. For the reasons emphasized under point 5 supra, the closest prior art is represented by document (D3). The problem to be solved is the provision of a further therapy for a diabetes type 2 patient in whom sulphonylurea administration alone does not suffice to normalise blood sugar levels. The proposed solution is the combination of a GLP-1 peptide and an oral hypoglycaemic agent which is a blocker of the ATP-dependent potassium channel on β -cells.
20. Document (D3), in the board's opinion, provided an incentive to use sulfonylureas in combination with GLP-1 peptides to treat the above category of patients. This is because the skilled person was taught by this

document that a combination of the above ingredients provided a greater β -cells stimulation, and hence insulin release, than a sulfonylurea alone, in these patients whose β -cells could still be sensitised, although normal blood sugar levels were not achieved. The skilled reader of document (D3) would have appreciated that even an additive response would be clinically worthwhile, in view of the expectation of an improved treatment vis-à-vis the treatment with a sulfonylurea alone, irrespective of any synergy which might be observed. Therefore, claim 1 of the auxiliary requests 1 and 2 lacks an inventive step and these requests are refused.

Auxiliary request 3

Article 123(2) EPC

21. The wording "...the treatment of type 2 diabetes is in a type 2 diabetic patient with secondary failure to sulphonylurea" in claim 1 of this request finds a basis in Example 2 of the published WO 93/18786 application.

Article 83 EPC

22. The respondent argues that the patent imposes an undue burden on the skilled person to identify all the synergistic combinations covered by claim 1 and that the patent in suit does not teach the reader how to obtain a synergistic response when the combination is administered by alternative routes.
23. However, claim 1 of this request is restricted to a medical use involving a combination of GLP-1(7-37) or GLP-1(7-36)amide with a sulfonylurea. The number of

possible combinations to be tested is thus limited and the insulinotropic activity can easily be tested by the skilled person, unlike in the situation dealt with in decision T 923/92 (OJ EPO 1996, 564, see point 27), where the board found insufficiency of disclosure. Moreover, no substantiation by way of verifiable facts has been provided by the respondent against the claimed "sulfonylurea" generalisation.

24. As for synergy, the board accepts that Example 2 of the patent in suit demonstrates synergy between GLP-1(7-37)amide and the sulfonylurea glibenclamide. Further, the board accepts that post published document (D11), taken as expert opinion, shows that combinations of GLP-1(7-36)amide with glibenclamide or tolbutamide, i.e. two different sulfonylureas, exhibit synergism. In the board's view, it is reasonable to conclude from the results of Example 2 (GLP-1(7-37)amide + glibenclamide) and from those of document (D11) (GLP-1(7-36)amide + glibenclamide or tolbutamide) that similar results will be obtained with other sulfonylureas, having in common the same mechanism of action and a similar chemical structure (see e.g. document (D3B), Diabeta[®] leaflet, third paragraph), the latter being decisive synergy factors prevailing, in the board's opinion, over e.g. the mode of administration.
25. In conclusion there is no basis for a finding of insufficiency of disclosure.

Article 56 EPC

26. Claim 1 of this request is now limited such that the patient suffering from type 2 diabetes is characterized

as "...a type 2 diabetic patient with secondary failure to sulphonylurea treatment", namely a patient who has been treated with sulfonylureas and got a failure due to β -cells' exhaustion, which, accordingly, are no longer able to produce and excrete insulin upon glucose stimulation.

27. The respondent maintains that Table 3 on page 6 of the patent ("glibenclamide = 10.6"; "control 1.6") shows that the patients still respond to sulfonylurea. However, these results relating to the insulinogenic indices (integrated insulin/integrated glucose) have to be balanced with those of Table 2 ("glibenclamide = 6.0; "control 6.0"), showing that glibenclamide does not achieve any increase in the concentration of blood glucose over the control. The board is therefore convinced that these patients do not react to a treatment with sulfonylurea.

Closest prior art and problem to be solved

28. The closest prior art is represented by document (D3) (see point 5 supra). The problem to be solved is the provision of a further therapy for a diabetes type 2 patient with secondary failure to sulfonylurea treatment. The proposed solution is the combination of GLP-1(7-37) or GLP-1(7-36) amide and a sulfonylurea.
29. The appellants maintain that at the priority date of the patent in suit, the skilled person would not expect any therapeutic advantage by administrating to a patient **suffering from a secondary failure** to sulfonylurea treatment with a further sulfonylurea or another agent stimulating the β -cell function, or with a

combination of these agents. It was thus unexpected, in the appellants' view, that **such a patient** could still be treated with the claimed combination of GLP-1(7-37) or GLP-1(7-36)amide and a sulfonylurea, owing to the surprising synergistic effect arising in such a combination (see also paragraphs [0027] and [0028] of the patent in suit).

The claimed subject matter would, in the board's view, be considered not obvious if an unexpected synergistic effect took place. In fact, since document (D3) does suggest an **additive** effect (see the term "additivity" at the end of document (D3)) and thus while this technical teaching was an incentive for the skilled to arrive at the subject matter of the main request and auxiliary requests 1 and 2 (see points 10 and 20 supra), the board accepts that the situation for the above identified subject matter is different, as the skilled person would not expect any therapeutic advantage by administering the combination disclosed in document (D3) to a patient who has been treated with sulfonylureas and got a secondary failure to sulfonylurea treatment due to β -cells' exhaustion.

The relevant issue is thus to establish whether a combination of GLP-1(7-37) or GLP-1(7-36)amide with a sulfonylurea exhibits the synergistic effect maintained by the appellants, but which the respondent denies.

Synergy

30. The patent in suit (see Tables 1, 2 and 3) and post-published documents (D8) and (D11) show a synergistic insulinotropic effect upon concomitant administration

of GLP-1(7-37)amide and glibenclamide or tolbutamide. Furthermore, Figure 2 of test report (D9) by Dr. Sturis shows a greater than additive effect for GLP-1(7-37) and glipizide. The data points for GLP-1(7-37) are above the dotted line which is the threshold above which a synergistic effect takes place. Dr. Sturis used as a control/baseline level of insulin secretion the worst possible approach for a demonstration of synergy, i.e. the peak insulin level observed during the 7 minute period preceding glipizide stimulation instead of a mean insulin value during this pre-incubation time lag.

Dr. Sturis obtained further confirmatory data in a second series of experiments (see document (D16)), wherein four treatment groups were included: controls, glipizide only, GLP-1 only, or a combination of glipizide with GLP-1 administered concomitantly to pancreas tissue. The figure under "Results" shows a marked and statistically significant synergistic effect on insulin secretion when a combination of glipizide and GLP-1 is used. This experiment also addresses the criticism raised by the respondent that in the experiment of document (D9), GLP-1(7-37) and glipizide were not administered concomitantly.

31. In view of the foregoing, the board is satisfied that a combination referred to in the use of claims 1 and 2, of GLP-1(7-37) or GLP-1(7-36)amide with a sulfonylurea exhibits an unexpected synergistic effect.

32. The respondent points to an inconsistency between the tests carried out according to document (D9) (7.5 nM glucose and 30 pM GLP-1(7-37)) and document (D16) (8 nM glucose, 56 pM GLP-1). However, the board finds this

difference in the concentration of one component (glipizide being 30 nM in both experiments) not fundamental as long as synergy is shown. If anything it shows that synergy is not confined to a punctual value.

33. The respondent questions the statistics underlying test report (D16) (see declaration (D19), which extends this criticism to documents (D9) and (D11)), by arguing that the reliance on a t-test to argue synergy requires that the data have to be consistent with a normal distribution and that this is not the case with the bar chart in document (D16), wherein the variability (ie standard deviations) is a function of the mean response.

However, the board observes that a respondent's expert (see Declaration (D21)) already considered the t-test as appropriate for evaluating the statistics underlying both Example 2 of the patent in suit and post-published document (D8), wherein the situation was the same as in test report (D16). Moreover, Dr. Sturis (see document (D16)), also used the Satterthwaite's approximation for the degrees of freedom, thus taking into account the different variances. In any case, the criticism raised in declaration (D19) has to be balanced with declaration (D18), which confirms that the statistical approach taken by Dr. Sturis in test report (D16) is reliable and valid and that the data support synergism.

34. Finally the respondent argues that test report (D16) at most demonstrates synergy in vitro between GLP-1 and glipizide without any implication regarding a possible effect in vivo.

However, the investigations described in document (D16) are ex vivo data in that the experimental set-up exploits whole organs removed from a body, not just cell-lines kept in suspension in a tube. As such, the set-up used by Dr. Sturis is highly representative of the in vivo situation. Furthermore, the single components were already known to the skilled person to be active and to lack toxicity in vivo on their own (for GLP-1(7-37): see document (D7); for sulfonylureas: see document (D17), page 277, r-h column). Neither did the respondent provide any evidence in support of the assertion that the in vivo effectiveness of the GLP-1 peptide could be reduced by the concurrent administration of a sulfonylurea, or that simultaneous administration of the two components could bear some risk due to potential interactions between the two drugs. Therefore this respondent's argument is also not convincing.

35. Thus the claims of this request also satisfy the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to maintain the patent on the basis of claims 1 and 2 of the third auxiliary request and a description to be adapted thereto.

The Registrar:

The Chairwoman:

P. Cremona

U.M. Kinkeldey