Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 11 June 2024

Case Number: T 2749/18 - 3.3.04

Application Number: 06839697.7

Publication Number: 1965823

IPC: A61K38/00, C07K1/00

Language of the proceedings: EN

Title of invention:
Methods for administering hypoglycemic agents

Patent Proprietor:
GlaxoSmithKline LLC

Opponents:
Novo Nordisk A/S
Sanofi
Generics [UK] Limited
Eli Lilly and Company

Headword:
GLP-1 agonists/GSK

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step (no), partial problems

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2749/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 11 June 2024

Appellant: (Patent Proprietor)	GlaxoSmithKline LLC 251 Little Falls Drive Wilmington, DE 19808 (US)
Representative:	Sagittarius IP Marlow International Parkway Marlow SL7 1YL (GB)
Respondent: (Opponent 1) - withdrwan -	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd (DK)
Representative:	Potter Clarkson Chapel Quarter Mount Street Nottingham NG1 6HQ (GB)
Respondent: (Opponent 2)	Sanofi 54 Rue La Boétie 75008 Paris (FR)
Representative:	Zwicker, Jörk ZSP Patentanwälte PartG mbB Hansastraße 32 80686 München (DE)
Respondent: (Opponent 3)	Generics [UK] Limited Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)

Respondent: (Opponent 4)	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 (US)
Representative:	Ingham, Stephen Howard Eli Lilly and Company Limited 8 Arlington Square West Downshire Way Bracknell, Berkshire RG12 1PU (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 4 October 2018 revoking European patent No. 1965823 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	O. Lechner
	M. Blasi
	A. Chakravarty
	L. Bühler

Summary of Facts and Submissions

I. The appeal by the patent proprietor (appellant) lies from the opposition division's decision to revoke European patent No. 1 965 823.

II. The patent was granted on European patent application No. 06 839 697.7, claiming priority of previous applications US 60/733,920 (filed on 4 November 2005) and US 60/742,600 (filed on 6 December 2005).
The application was filed as an international patent application published as WO 2007/056681 (application as filed).

III. In its decision, the opposition division held that the sets of claims according to the main request (filed by letter of 27 July 2017) and auxiliary requests 3, 5 and 6 added subject-matter within the meaning of Article 123(2) EPC.
The subject-matter claimed in auxiliary request 1 was found to lack novelty under Article 54 EPC.
The subject-matter claimed in auxiliary requests 2 and 4 was found to lack an inventive step under Article 56 EPC.
Auxiliary requests 7 and 8 were not admitted into the proceedings.
The opposition division also found that the appellant was entitled to the priority right and that the claims of auxiliary request 1 enjoyed priority from the second priority application, i.e. the effective date was 6 December 2005.

IV. With its statement of grounds of appeal, the appellant filed sets of claims according to a main request and auxiliary requests 1 to 6.

V. Opponents 2, 3 and 4 (respondents 2, 3, and 4) replied to the statement of grounds of appeal. Opponent 2 submitted document D71.

VI. Opponent 1 withdrew its opposition by letter dated 2 May 2019. In the absence of any issues other than those related to the patent in suit, it ceased to be a party to the appeal proceedings.

VII. After issue of the board's communication pursuant to Article 15(1) RPBA, the parties made the following submissions.

By letter of 22 May 2024, respondent 2 announced that it would not attend the oral proceedings but that it maintained all requests and objections made in writing.

By letter dated 3 June 2024, the appellant withdrew the main request and auxiliary request 2 as filed with the statement of grounds of appeal. Auxiliary request 1 filed with the statement of grounds of appeal thus became the main request, and auxiliary request 3 to 6 filed with the statement of grounds of appeal became auxiliary requests 1 to 4.

VIII. The oral proceedings before the board took place on 11 June 2024.

Respondent 2 did not attend the oral proceedings but maintained its written submissions. It had notified the board in writing of its non-attendance. Respondent 2 was treated as relying on its written case, in line with Rule 115(2) EPC and Article 15(3) RPBA.

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

IX. Claim 1 of the main request reads:

"1. A Glucagon-like peptide (GLP-1) agonist composition comprising at least one polypeptide having GLP-1 activity for use in a method of treatment of Type 1 diabetes, Type II diabetes, obesity or hyperglycemia, characterized in that the composition is subcutaneously administered via an injection device comprising a tube having a needle gauge of 28 or greater and wherein said composition is administered once weekly, and further wherein said composition comprises 0.25 mg to 104 mg of said polypeptide having GLP-1 activity."

Claim 1 of auxiliary request 1 reads:

"1. A Glucagon-like peptide (GLP-1) agonist composition comprising at least one polypeptide having GLP-1 activity and wherein said at least one polypeptide comprises a conjugate of GLP-1 or a conjugate of a GLP-1 variant or a conjugate of a GLP-1 fragment for use in a method of treatment of Type 1 diabetes, Type II diabetes, obesity or hyperglycemia, characterized in that the composition is subcutaneously administered via an injection device comprising a tube having a needle gauge of 28 or greater and wherein said composition is administered once weekly, and further wherein said composition comprises 0.25 mg to 104 mg of said polypeptide having GLP-1 activity."

Claim 1 of auxiliary request 2 reads:

"1. A Glucagon-like peptide (GLP-1) agonist composition comprising at least one polypeptide having GLP-1

activity and wherein said at least one polypeptide comprises a conjugate of GLP-1 or a fragment, or variant thereof, for use in a method of treatment of Type 1 diabetes, Type II diabetes, obesity or hyperglycemia, characterized in that the composition is subcutaneously administered via an injection device comprising a tube having a needle gauge of 28 or greater and wherein said composition is administered once weekly, and further wherein said composition comprises 0.25 mg to 32 mg of said polypeptide having GLP-1 activity."

Claim 1 of auxiliary request 3 reads:

"1. A Glucagon-like peptide (GLP-1) agonist composition comprising at least one polypeptide having GLP-1 activity and wherein said at least one polypeptide comprises a conjugate of GLP-1 or a conjugate of a GLP-1 variant or a conjugate of a GLP-1 fragment for use in a method of treatment of Type 1 diabetes, Type II diabetes, obesity or hyperglycemia, characterized in that the composition is subcutaneously administered via an injection device comprising a tube having a needle gauge of 28 or greater and wherein said composition is administered once weekly, and further wherein said composition comprises 0.25 mg to 32 mg of said polypeptide having GLP-1 activity."

Claim 1 of auxiliary request 4 reads:

"1. A Glucagon-like peptide (GLP-1) agonist composition comprising at least one polypeptide having GLP-1 activity which comprises SEQ ID NO 1, for use in a method of treatment of Type 1 diabetes, Type II diabetes, obesity or hyperglycemia, characterized in that the composition is subcutaneously administered via

an injection device comprising a tube having a needle gauge of 28 or greater and wherein said composition is administered once weekly, and further wherein said composition comprises 0.25 mg to 32 mg of said polypeptide having GLP-1 activity."

X. Reference is made to the following documents:

D4: R. Caffrey and J. Seley, Diabetes Health - Investigate Inform, Inspire, 1 November 2004, URL: http://www.diabeteshealth.com/read/2004/11/01/4128/how-to-take..., 3 pages

D5: M. Miller et al., Langmuir 26(2), 2010, 1067-74

D11: WO 2004/060920 A1

D13: H. Harder et al., Diabetes care 27(8), 2004, 1915-21

D14: WO 03/099314 Al

D18: WO 2005/077042 A2

D19: WO 02/46227 A2

D20: US 7,452,966 B2

D26: WO 2005/000892

D47: K. Degn et al., Diabetes 53(5), 2004, 1187-94

D48: L. Baggio et al., Diabetes 53(9), 2004, 2492-500

D51: British Standard BS EN ISO 9626:1995, as of 31 January 2002, 18 pages

D53: V. Niblett, A Nurse's Guide to Dosage Calculation - Giving Medications Safely, Lippincott Williams & Wilkins, 2006, 134

D61: R. Teschemacher, Opinion in the opposition proceedings concerning European patent 1 965 823 on the requirement of novelty for a further medical use, dated 22 February 2018, 21 pages (including CV and list of publications)

D64a: Handbook of Nonprescription Drugs, 8th edn., ed. E.G. Feldman and D.E. Davidson, 1986, 287

D64b: Handbook of Nonprescription Drugs, 14th edn., ed. R. Berardi, 2004, 1090-1

XI. The appellant's arguments relevant to the decision can be summarised as follows.

(a) Main request – Inventive step – Article 56 EPC – claim 1

Closest prior art

Document D26 was the closest prior art. It disclosed specific glucagon-like peptide 1 (GLP-1) analogues fused to specific IgG4-Fc derivatives.

Differentiating feature, its technical effect and the objective technical problem

The subject-matter of claim 1 differed from the subject-matter of claim 19 of document D26 in that the GLP-1 analogue composition was administered:

- by subcutaneous (s.c.) administration
- via an injection device comprising a tube having a needle gauge of 28 or greater
- at a dose of 0.25 to 104 mg

The technical features of claim 1 worked together to provide the combined effect of a less burdensome, including a less painful, treatment of type 1 diabetes, type 2 diabetes, obesity or hyperglycaemia. The features thus had to be considered together.

The objective technical problem was the provision of a GLP-1 agonist composition for use in the treatment of the specified diseases that has an improved method of administration which is both less burdensome and less painful.

Obviousness

Even if the four technical features - a dose of 0.25 to 104 mg, a once-weekly administration, s.c. administration and administration via an injection device comprising a tube having a needle gauge of 28 or greater - had been known individually, it would not have been obvious to combine them in one treatment. Neither document D26 nor any of the cited prior-art documents disclosed or pointed in the direction of the claimed combination.

Document D26 did not disclose each feature of claim 1 as a preferred embodiment, thus the skilled person would not have extracted and combined them from the disclosure as a whole.

Page 20, lines 3 to 12 of document D26 offered various administration routes, including intravenous,

intramuscular (i.m.), s.c. and intraperitoneal. S.c. administration was not disclosed as preferred. The examples disclosed only a single s.c. administration, not a once-weekly schedule. Moreover, a reference to s.c. administration in an animal model could hardly be evidence of a preference in human treatment.

Documents D13 and D47 disclosed a daily dosing of the GLP-1 analogue liraglutide. Thus, the skilled person would not have considered their teaching to be applicable for a treatment directed to a once-weekly administration.

Moreover, document D26 was incompatible with the teaching of document D13, which focused on once-daily administration of liraglutide - a modified GLP-1 molecule attached to a fatty-acid moiety that binds to albumin *in vivo*, forming the fusion protein post-administration.

Without knowledge of the claimed invention, the skilled person would not have had concerns regarding injection site pain for the fusion proteins disclosed. Document D26 did not suggest making changes to reduce injection site pain.

In the absence of such concerns, the logical approach for administering the fusion protein of document D26 as an s.c. injection would have been to use 25- to 27-gauge needles. These needle diameters were preferred for human administration as evidenced by document D53, which reflected the general practice at the time of the invention.

Document D5 evidenced that the prior art taught away from using thin needles due to concerns about the high

viscosity of solutions with larger proteins, particularly protein conjugates. Document D53 taught that small-gauge needles bend very easily. No references demonstrated the s.c. delivery of any high molecular weight protein using a needle gauge of 28 or greater.

Without knowledge of the current invention, nothing in document D26 would have motivated the skilled person to consider document D48. This document was irrelevant as it related to intracerebroventricular and not s.c. injection of the GLP-1 analogue albugon (also known as albiglutide) - which was identical to the protein of SEQ ID NO 1 of the patent in suit, as also acknowledged by the appellant.

Prior-art documents D4, D64a and D64b were also irrelevant since they concerned administration of insulin, not GLP-1 agonists, while document D26 pertains to GLP-1 fusion proteins. Insulin was different to a GLP-1 analogue and not administered once per week only.

Finally, other prior art demonstrated alternative ways to address injection pain, such as slow-release infusions (document D14, page 3, line 26 to page 4, line 1) or infusion pumps (documents D11, D19 and D20) as alternatives to pen-like syringes.

(b) Auxiliary requests 1 to 3 - Inventive step - Article 56 EPC - claim 1

For auxiliary requests 1 to 3, no independent argument on inventive step under Article 56 EPC was put forward.

(c) Auxiliary request 4 - Inventive step - Article 56 EPC - claim 1

Closest prior art

Document D26 could be considered to represent the closest prior art.

Differentiating feature, its technical effect and the objective technical problem

Claim 1 specified the same administration regimen to treat the diseases as claimed in the main request, with the additional difference that the GLP-1 agonist used was SEQ ID NO 1, which was the amino acid sequence of albiglutide.

As argued for the main request, the distinguishing features did not operate in isolation, they were key components of the administration method claimed for the treatment of the specified diseases and together achieved the technical effect of an improved administration method for, in this case, a specific GLP-1 agonist that was both less burdensome and reduced pain for the patient.

The objective technical problem was the provision of a GLP-1 agonist composition for use in treatment of type 1 diabetes, type 2 diabetes, obesity or hyperglycaemia that has an improved administration that is both less burdensome for the patient and reduces pain for the patient.

Obviousness

Even a combination of the disclosure of document D4, D13, D64a or D64b with that in document D26 would not have motivated the use of a needle gauge of 28 or greater for administering the specific GLP-1 agonist according to SEQ ID NO 1. As argued for the main request, the skilled person would not have turned to prior art on insulin delivery, such as document D4, D64a or D64b, or document D13, which pertained to the non-fusion GLP-1 agonist liraglutide.

Even if these references had been combined with the disclosure of document D26, they would not have prompted the skilled person to use a needle gauge of 28 or greater for administering a polypeptide according to SEQ ID NO 1.

Additionally, while document D18 disclosed SEQ ID NO 1, it did not provide any rationale for using a needle gauge of 28 or greater. The general practice and logical approach would have been to use a needle gauge of 25 to 27, as evidenced by document D53.

Example 7 of document D26 showed that administration of higher doses of GLP-1 agonistic polypeptide resulted in higher insulin production. This was a clear incentive to administer higher doses of the insulinotropic GLP-1 agonists. Instead, the dose range for the composition according to claim 1 of auxiliary request 4 had been narrowed to 0.25 to 32 mg. The selection of a narrower dose range would not have been obvious to the skilled person given the data in Example 7 of Document D26. On the contrary, the skilled person would have had an incentive to administer higher doses of the polypeptide

with GLP-1 activity to achieve higher levels of insulin.

None of the prior-art documents at hand taught or suggested the claimed subject-matter.

XII. The respondents' arguments relevant to the decision can be summarised as follows.

(a) Main request - Inventive step - Article 56 EPC - claim 1

Closest prior art

Document D26 represented the closest prior art.

Differentiating feature, its technical effect and the objective technical problem

The subject-matter of claim 1 differed from the subject-matter of claim 19 of document D26 at least by the feature:

- administered via an injection device comprising a tube having a needle gauge of 28 or greater

Other differences addressed and partly recognised by the respondents at different points in the proceedings are as follows:

- s.c. administration
- the dose of 0.25 to 104 mg

Although a needle gauge of 28 or greater was not a limiting feature, it was dealt with for the sake of argument.

Document D26 as a whole disclosed s.c. administration of GLP-1 agonistic polypeptides to animals, including cynomolgus monkeys (Examples 3 to 7). This animal model closely resembled humans, indicating to the skilled person that s.c. administration was the intended route for human therapy. Thus, this feature could be read into claim 19 of document D26.

Respondent 3 considered the needle gauge and the dose to be differences.

Respondent 4 argued that the claimed dose range was implicitly disclosed by the dose ranges on page 21, lines 18 to 19 of document D26 (i.e. 0.01 to 1 mg/kg or 0.05 to 0.5 mg/kg body weight), which also fell within the claimed range of 0.25 to 104 mg.
Thus, the needle gauge of 28 or greater was the only difference when considering the disclosure of document D26 as a whole.

The patent in suit did not link the needle gauge to any specific effect. It was common general knowledge that a greater needle gauge was associated with reduced injection site pain.

On the other hand, the frequency of dosing, not the needle gauge, determined whether the treatment was less burdensome.

The application as filed provided no working examples to support a less painful treatment. Therefore, plausibility for the claimed solution - the needle gauge of 28 or greater - relied merely on the common general knowledge that a thin needle causes less pain.

Respondent 2 defined the objective technical problem as the provision of a GLP-1 agonist composition for the treatment of diabetes using a mode of once-weekly s.c. administration which minimises injection site pain.

Respondent 3 argued that the patent in suit did not provide any evidence of a synergy between the features s.c. administration, a dose of 0.25 to 104 mg, once-weekly administration and a needle gauge of 28 or greater. Thus, there was no combination invention, and it was necessary to define partial problems. Starting from the subject-matter of claim 19 of document D26, the problem solved by:

- the dose was an alternative treatment
- the claimed needle gauge was the provision of a less painful method of treatment

Respondent 4 defined the objective technical problem in the appellant's favour as how to implement the teaching of document D26 to provide low injection pain.

Obviousness

Starting from the overall teaching of document D26 and considering the skilled person's common general knowledge, the claimed subject-matter was obvious.

It was common general knowledge that a needle gauge of 28 or greater was linked to reduced injection site pain. This knowledge extended to the delivery of various polypeptides used in diabetes treatment, including insulin (e.g. D4, D64a and D64b), as well as GLP-1 agonists (e.g. D47 and D13). The European Standard EN ISO 9626:1996 (D51) even specified needles with a gauge as fine as 33.

Using a needle with a gauge known for being associated with reduced injection site pain was obvious.

Post-published document D53, a guideline for nurses, reported that small-gauge needles bend easily. However, this document was irrelevant since it did not pertain to diabetic patient treatment and did not involve needles with a gauge of 28 or greater. Documents D4, D13, D47, D64a and D64b used small-gauge needles for diabetic patients.

Similarly, post-published document D5, which stated that high-viscosity solutions could not be administered with 25- to 27-gauge needles, did not need to be taken into consideration since the viscosity is not a feature of claim 1. Furthermore, prior-art document D48 showed that there were no issues administering the large GLP-1-albumin recombinant protein albugon using a 30-gauge needle.

(b) Auxiliary requests 1 to 3 - Inventive step - Article 56 EPC - claim 1

The amendments made to auxiliary requests 1 to 3 did not overcome the finding of lack of inventive step. Claim 1 of auxiliary requests 1 to 3 lacked an inventive step for the same reasons as for the main request as the use of the term "conjugates" did not add an additional distinguishing feature compared to document D26, which also described the fusion of proteins.

(c) Auxiliary request 4 - Inventive step - Article 56 EPC - claim 1

The amendments filed with auxiliary request 4 failed to overcome the finding of lack of inventive step for claim 1 of the main request.

Document D26 represented the closest prior art.

The subject-matter of claim 1 of auxiliary request 4 differed from the subject-matter of claim 19 of document D26 by the features:

- the dose of 0.25 to 32 mg
- the GLP-1 analogue being one according to SEQ ID NO 1

This is in addition to the different features already identified between claim 1 of the main request and the disclosure in document D26.

The arguments given for claim 1 of the main request applied equally, and in addition no technical effect had been disclosed in the application as filed for a GLP-1 analogue according to SEQ ID NO 1 going beyond what had already been known in the prior art.

Respondent 2 considered the partial objective technical problem due to the additional feature of the GLP-1 agonist being one according to SEQ ID NO 1 as the provision of an alternative GLP-1 agonist for the treatment of diabetes (and other diseases).

Respondent 3 argued that in view of the amendment to SEQ ID NO 1, a further partial problem had to be formulated in addition to those defined for the main request. This problem was the provision of an alternative treatment for diabetes and other diseases.

Respondent 4 defined the objective technical problem as it had for the main request, being the implementation of the teaching of document D26 to provide low injection pain.

A skilled person seeking alternative GLP-1 agonists would have considered document D18 - which disclosed the GLP-1 albumin fusion protein albiglutide - as an alternative to document D26 and the GLP-1-Fc fusion protein it disclosed. Alternatively, the opposition division had considered that document D48, which also disclosed albugon (identical to albiglutide being encoded by SEQ ID NO 1), disclosed another obvious alternative.

The appellant's objection that document D18 did not make the treatment with a GLP-1 analogue according to SEQ ID NO 1 plausible was irrelevant since the patent in suit did not show any technical effect for this either.

XIII. The parties' requests relevant to the decision were as follows.

(a) The appellant requested that:
- the opposition division's decision to revoke the patent be set aside and that the patent be maintained in amended form on the basis of the set of claims of the main request or, alternatively, auxiliary requests 1 to 4

(b) Respondent-opponent 2 requested that:
- the appeal be dismissed and that the patent be revoked
- auxiliary request 3 not be admitted

(c) Respondent-opponent 3 requested that:
- the appeal be dismissed and that the patent be revoked

(d) Respondent-opponent 4 requested that:
- the appeal be dismissed and that the patent be revoked
- auxiliary requests 1 and 3 not be admitted
- any remittal to the opposition division to consider sufficiency of disclosure be avoided

Reasons for the Decision

Main request

Inventive step - Article 56 EPC - claim 1

Closest prior art

1. It is common ground that document D26 represents the closest prior art for the claimed subject-matter.

2. Document D26 discloses GLP-1 variants fused to specific IgG4-Fc derivatives, which are conjugated GLP-1 variants with an extended serum half-life compared to the unconjugated polypeptide having GLP-1 activity, for the treatment of type 1 and type 2 diabetes (diabetes mellitus), obesity, and other diseases (page 1, paragraphs 1 and 2 and page 4, paragraph 2) by administration via any route including, for example, i.m. and s.c. (page 20, paragraph 2), at a dose of 0.01 to 1 mg/kg or 0.05 to 0.5 mg/kg, once every two weeks, once a week or, if necessary, two to three times per week (page 21, lines 18 to 23). The drug can be injected with a sterile syringe or other mechanical device such as an infusion pump (page 20, paragraph 2).

Claim 18 discloses administration of a dose between about 0.05 to 0.5 mg/kg.

Claim 19 discloses a once-weekly administration for treating non-insulin dependent diabetes mellitus or inducing weight loss in an overweight patient. The *in vivo* examples in document D26 provide glucose tolerance tests in rats (Example 3), pharmacokinetic (Example 5) and pharmacodynamic (Example 6) studies in cynomolgus monkeys, and pharmacodynamic studies in rats (Example 7) where the GLP-1 fusion protein is s.c. administered to the (apparently healthy) animals.

In light of the purpose and technical features in common, the disclosure of claim 19 can therefore be taken to represent the closest prior art for the assessment of inventive step under the problem-solution approach.

Differentiating feature, its technical effect and the objective technical problem

3. It was a matter of dispute between the appellant and the respondents whether the needle diameter characterising a device used in a therapeutic method could be taken into account as a feature of a "specific" use within the meaning of Article 54(5) EPC (see also document D61).

4. The board has doubts that a device-related technical feature, in the current case the "injection device comprising a tube having a needle gauge of 28 or greater", can be taken into consideration as a feature of the claimed subject-matter if it has not been convincingly shown that this feature directly interacts with the substance or composition (in the current case,

the glucagon-like peptide agonist composition) in a manner that alters the treatment (in this case, the treatment of type 1 diabetes, type 2 diabetes, obesity or hyperglycaemia) as such.

However, it was not necessary for the board to consider this issue further because the decision on that point is based on the assumption in the appellant's favour that the feature "injection device comprising a tube having a needle gauge of 28 or greater" could indeed be taken into account.

5. The subject-matter of claim 1 of the main request differs from the subject-matter of claim 19 of document D26 in that the polypeptide having GLP-1 activity is administered:

- at a dose of 0.25 to 104 mg
- by the s.c. route
- via an injection device comprising a tube having a needle gauge of 28 or greater

6. The appellant argued that the four features of claim 1 — s.c. administration, administration via an injection device with a needle gauge of 28 or greater, once-weekly administration and a dose of 0.25 to 104 mg — acted as a true combination resulting in reduced pain, leading to a less burdensome treatment.

7. The only mention of either minimising burdensome regimens or injection site pain is in the background section on page 1, paragraph 2 of the application as filed. It discloses that insulin and insulinotropic peptides may be administered via s.c. injection, such as with a needle-containing device, and that patients

may need to inject several times a day to control blood glucose, which can be burdensome as well as painful.

However, from this background section, it is not clear which of the several technical features - less frequent injection, dose of the drug and/or needle with a gauge of 28 or greater - was in fact considered to be associated with a less burdensome and/or less painful treatment.

In the appellant's favour and as conceded by the respondents, the board accepts that the claimed needle gauge of 28 or greater is linked to a less painful and less burdensome administration.

The examples of the application as filed do not show any therapeutic effect beyond what was already known in the prior art. Dosage regimens or pain are not addressed in any of the examples. Moreover, none of the examples discloses a technical effect related to the needle diameter.

The board thus concludes that there is no teaching of a combined effect of the above-mentioned differences between the claimed subject-matter and that disclosed in claim 19 of document D26. The technical features that differentiate the claimed subject-matter from the closest prior art are seen as an aggregation of features, and each of them has to be assessed separately.

In summary, no combined effect resulting from a functional reciprocity based on a combination of the individual technical features, in the sense of a mutual influence on their respective operation, is discernible. It is therefore appropriate to define

partial problems (Case Law of the Boards of Appeal, 10th edn., 2022, I.D.9.3.2).

8. Thus, the objective technical problem consists of the following partial problems:
- determination of a dose for a GLP-1 agonist for use in the treatment of type 2 diabetes
- determination of a route of administration for a GLP-1 agonist for use in the treatment of type 2 diabetes
- determination of an administration mode that minimises pain in the administration of a GLP-1 agonist for use in the treatment of type 2 diabetes

Obviousness

9. Starting from the subject-matter of claim 19 of document D26 and seeking a solution to the three partial problems defined above (see point 8.), the skilled person would have administered the GLP-1 agonist composition comprising a GLP-1 fusion protein via the s.c. route at a dose falling within the claimed range by implementing the suggestions made in document D26.

9.1 Claim 18 and also page 21, lines 18 to 19 of document D26 disclose doses of 0.05 to 0.5 mg/kg for treating non-insulin dependent diabetes mellitus, i.e. type 2 diabetes. This dose range translates into effective doses that fall within the range of 0.25 to 104 mg specified in claim 1, considering a standard body weight of approximately 70 kg for an adult human patient, as submitted by respondent 4. Furthermore, the board considers that determination of an appropriate dose was routine for the skilled person, this being common general knowledge at the relevant date.

9.2 Page 20, paragraph 2 of document D26 lists different theoretically feasible administration routes, including s.c. administration. However, Examples 3, 4, 6 and 7 of document D26, which provide *in vivo* pharmacokinetic and pharmacodynamic studies in rats and cynomolgus monkeys, exclusively employ the s.c. route. Although claim 1 is not limited to the treatment of humans, the use of an administration route in *in vivo* experiments with primates suggests that this route is suitable for human therapy. This is because cynomolgus monkeys are commonly used in biomedical research because their physiological and genetic similarities to humans are well-established general knowledge.

10. Even if document D26 does not mention that site injection pain could be an issue, it was part of the common general knowledge in diabetes treatment that a smaller needle diameter, such as a needle gauge of 28, was a factor capable of reducing pain at the injection site (see documents D4, D13, D47, D64a and D64b, with further details below). Thus, the skilled person would have considered administration via an injection device comprising a tube having a needle gauge of 28 or greater. Implementation of these features was a routine measure for the skilled person.

10.1 Document D4 teaches on page 2, paragraph "*2. Needle Gauge*" that insulin syringe needles are thinner than ever before and available in gauges of 28, 29, 30 and 31. It states that "*[m]any people prefer the thinner needles since this provides a more comfortable injection*".

10.2 Document D13 investigates the effect of liraglutide, a long-acting GLP-1 derivative, on glycaemic control, body composition and 24-h energy expenditure in

patients with type 2 diabetes. Liraglutide was administered in the abdomen or the thigh using a NovoPen 1.5 with a Novofine 30-gauge 0.3 to 8 mm needle as the dispensing device (title and page 1916, middle column, line 16 ff).

10.3 Document D47 shows that one week's treatment with the long-acting GLP-1 derivative liraglutide markedly improves 24-h glycaemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes (abstract). 6 g/kg body weight liraglutide was injected s.c. into the abdomen once daily for 9 days using a "*NovoPen (1.5 with Novofine 30-G, 0.3- to 8-mm needle) as the dispensing device*" (see page 1188, "*Experimental designs*").

10.4 Document D64a discloses that the needle sizes recommended for diabetic patients for s.c. insulin injection are in the 25- to 28-gauge range. It is also mentioned that once patients use the thinner 27- to 28-gauge needles, it is difficult to get them to return to the 25-gauge needles due to less pain at the injection site.

Document D64b teaches on page 1090, left column, last paragraph entitled "*Types of Syringes*" that the smaller (28- to 30-gauge) needles cause less pain.

11. The appellant argued that the examples in document D26, relating to s.c. injection, would not have been considered relevant by the skilled person since they concerned a single administration and not a once-weekly administration as claimed. Document D13, on page 1916 and document D47 on page 1187, right-hand column of the abstract, disclosed daily dosing of the GLP-1 analogue liraglutide.

12. The board considers that even though the examples in document D26 relate to a single s.c. injection and documents D13 and D47 relate to once-daily administration of GLP-1 analogues, this does not mean that the skilled person would have disregarded their teaching on the administration route or measures for reducing injection site pain in the treatment of diabetes in general, including treatment with GLP-1 analogues.

Regardless of the medicament, each individual administration causes pain, and while the number of administrations may affect compliance, it does not influence the amount of pain perceived during an injection.

13. The appellant also argued that post-published documents D5 and D53 showed that, even some years after the filing date of the patent in suit, the preferred needle size for humans was still one with a gauge between 25 to 27. Document D53 explicitly stated that it would be best to use a small-gauge needle - 26 or 27 gauge - for most s.c. injections as these cause the least tissue trauma. A disadvantage of small-gauge needles was that they bend very easily (document D53, page 134, paragraph 2). Thus, the skilled person was discouraged from selecting a needle gauge greater than 27.

14. The board is not persuaded by this argument. Documents D5 and D53 are post-published and do not relate to the treatment of diabetes.

Thinner needles provide less injection pain but were known, as disclosed in document D53, to bend more easily. The claimed subject-matter relates to the use of a thinner needle to achieve better patient comfort

but does not address or solve the bending issue. In other words, the bending risk remains, and the claimed subject-matter does not make any contribution to overcome this problem.

15. Therefore, the board does not accept that there was a disincentive or a teaching away from the use of high-gauge needles at the effective date of the patent for s.c. administration in the treatment of diabetes, e.g. for administration of GLP-1 peptide analogues.

16. Regarding the appellant's argument that the skilled person would not have turned to the teaching of prior art documents D4, D64a and D64b because these documents concern insulin and not GLP-1 agonists, the board considers that the skilled person in the field of metabolic diseases such as diabetes and obesity would have also relied on common general knowledge relating to the s.c. injection of insulin. This is because both treatments are for the same group of patients, and the therapeutic effects of GLP-1 agonists include insulinotropic effects. Moreover, for the objective technical problem formulated in point 8. above, the skilled person's focus would have been on the advantages and disadvantages of various needle gauges for s.c. injection, not on the agent injected.

17. The appellant also argued that the skilled person would have been aware of alternative methods to address injection pain, such as slow-release infusions (document D14, page 3, line 26 to page 4, line 1) or infusion pumps (documents D11, D19 and D20), instead of pen-like syringes. However, the existence of other obvious solutions to the objective technical problem cannot establish an inventive step for subject-matter that is otherwise obvious.

18. Thus, the subject-matter of claim 1 does not involve an inventive step within the meaning of Article 56 EPC in view of the teaching in document D26 and the skilled person's common general knowledge.

Auxiliary requests 1 to 3

Admittance - Article 12(4) RPBA 2007

19. In view of the board's decision on inventive step under Article 56 EPC (see below), it is not necessary to provide reasons for the admittance of auxiliary requests 1 and 3.

The claimed subject-matter

20. The subject-matter of claim 1 of auxiliary request 1 differs from that of claim 1 of the main request in that the glucagon-like peptide (GLP-1) agonist composition comprising at least one polypeptide having GLP-1 activity is further characterised by the feature "and wherein said at least one polypeptide comprises a conjugate of GLP-1 or a conjugate of a GLP-1 variant or a conjugate of a GLP-1 fragment".

21. The subject-matter of claim 1 of auxiliary request 2 differs from that of claim 1 of the main request in that (i) the at least one polypeptide having GLP-1 activity comprises a conjugate of GLP-1 or a fragment or variant of it and (ii) the dose range for the polypeptide having GLP-1 activity is narrowed to a range of 0.25 to 32 mg (compared to 0.25 to 104 mg in claim 1 of the main request).

22. The subject-matter of claim 1 of auxiliary request 3 differs from that of claim 1 of the main request in

that (i) the at least one polypeptide having GLP-1 activity comprises a conjugate of GLP-1 or a conjugate of a GLP-1 variant or a conjugate of a GLP-1 fragment and (ii) the dose range for the polypeptide having GLP-1 activity was narrowed to a range of 0.25 to 32 mg (compared to 0.25 to 104 mg in claim 1 of the main request).

Inventive step - Article 56 EPC - claim 1

23. Document D26 represents the closest prior art (for a summary, see point 2. above).

24. The further ways of characterising the at least one polypeptide having GLP-1 activity in claim 1 of auxiliary requests 1 to 3 do not represent a further distinguishing feature in view of the conjugated GLP-1 variants disclosed in document D26.

25. The effective doses resulting from the narrower dose range of 0.25 to 32 mg for the at least one polypeptide with GLP-1 activity, as specified in claim 1 of auxiliary requests 2 and 3, represent a difference to the closest prior art, as does the broader range of 0.25 to 104 mg in claim 1 of the main request and auxiliary request 1 (see point 5. above). However, they still overlap with the dose range of 0.05 to 0.5 mg/kg disclosed in claim 18 of document D26.
Just as no technical effect was demonstrated for the broader dose range of 0.25 to 104 mg, none has been shown for the narrower dose range of 0.25 to 32 mg in the application as filed.

Thus, the specified dose ranges cannot render the subject-matter of claim 1 of auxiliary requests 1 to 3 inventive over the disclosure of document D26 for the

same reasons as provided for claim 1 of the main request above (see points 5. to 16., in particular point 9.1).

26. Consequently, the board considers that the subject-matter of claim 1 of auxiliary requests 1 to 3 also lacks an inventive step under Article 56 EPC for the same reasons as provided for claim 1 of the main request above (see points 5. to 16.).

Auxiliary request 4

Inventive step - Article 56 EPC - claim 1

Closest prior art

27. Document D26 represents the closest prior art for the subject-matter of claim 1 of auxiliary request 4.

Differentiating feature, its technical effect and the objective technical problem

28. The subject-matter of claim 1 of auxiliary request 4 differs from the subject-matter of claim 19 of document D26 in that the polypeptide having GLP-1 activity according to claim 1 of auxiliary request 4:
- comprises SEQ ID NO 1, i.e. two tandemly oriented GLP-1(7-36)(A8G) polypeptides N-terminally fused to human serum albumin
- is administered at a dose of 0.25 to 32 mg
- is administered by the s.c. route
- is administered via an injection device comprising a tube having a needle gauge of 28 or greater

29. The application as filed does not reveal any new or additional technical effect of using a polypeptide with

SEQ ID NO 1 other than its established GLP-1 activity. The overall effect of conjugating GLP-1 polypeptides to albumin is an extended serum half-life, an effect already disclosed for the GLP-1-Fc conjugates of document D26.

30. For the administration by the s.c. route and administration via an injection device comprising a tube having a needle gauge of 28 or greater, the same considerations apply as for the main request given in point 7. above.

Concerning the narrower dose range of 0.25 to 32 mg of the at least one polypeptide having GLP-1 activity, the same considerations on inventive step apply as for the main request (see point 9.1 above).

31. As for the main request, no combined effect resulting from a functional reciprocity based on a combination of the individual technical features of claim 1, in the sense of a mutual influence on their respective operation, is discernible. Thus, the various differences between the closest prior art and the claimed subject-matter must be assessed separately, and it is therefore appropriate to define partial problems for each difference.

32. Thus, the partial problems to be solved by the claimed subject-matter are the same as those formulated for claim 1 of the main request with the additional partial objective technical problem of providing an alternative conjugated GLP-1 agonist for use in the treatment of type 2 diabetes.

Obviousness

33. In searching for an alternative polypeptide with GLP-1 activity with an extended serum half-life, the skilled person would have taken into account the relevant prior art and considered the disclosure of document D18.

34. Document D18 discloses that therapeutic proteins administered *in vivo* may have short plasma stability due to rapid clearance, necessitating more frequent or higher doses, which often leads to increased injection site reactions, side effects and toxicity (see paragraph [0006]). The proposed solution to this problem is to enhance plasma stability by fusing the proteins with albumin.

Paragraph [0057] discloses GLP-1-human serum albumin (HSA) fusion proteins monomers or tandem proteins for regulating glucose levels in diabetic patients. Fasted diabetic db/db mice are s.c. administered either the monomer or tandem GLP-1-HSA fusion protein for oral glucose tolerance tests. The GLP-1 (7-36, A8G)2x-HSA (CID 3610) (see Figure 11, SEQ ID NO 319), which comprises SEQ ID NO 1 as claimed in claim 1 of auxiliary request 4, significantly reduced blood glucose at 6 and 24 h after s.c. injection when compared to monomeric GLP-1 (7-36, A8G)-HSA fusion (see Figure 11 and paragraph [0057]). Paragraphs [0442] to [0447] outline general dosage guidelines for parenteral administration of albumin fusion proteins. On consulting document D18, the skilled person would have arrived at using a polypeptide having GLP-1 activity comprising SEQ ID NO 1.

35. The appellant also argued that based on the data in Example 7 of document D26 showing higher amounts of

insulin produced in response to higher doses, the skilled person would have adjusted the dose range towards higher doses rather than narrowing it towards lower doses as specified in claim 1 of auxiliary request 4.

Example 7 describes a pharmacodynamic study following a single subcutaneous injection of a GLP-1 fusion protein. The board considers that, in determining a dosage for repeated, once-weekly administration, the skilled person would not overly rely on the single-administration data from Example 7. Instead, they would use the dose ranges disclosed on page 21 as a basis for determining a suitable dosage for repeated use through routine experimentation.

36. The claimed subject-matter also represents an obvious solution for each of the other partial problems set out above, when starting from the teaching of closest prior-art document D26 and taking the skilled person's common general knowledge into account, for the reasons provided for claim 1 of the main request (see points 9. to 16. above).

37. In view of the above considerations, the subject-matter of claim 1 of auxiliary request 4 lacks an inventive step (Article 56 EPC).

38. Thus, no claim request is allowable, and the appeal must be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

K. Boelicke M. Pregetter

Decision electronically authenticated