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Datasheet for the decision of 26 June 2024

Case Number: T 1404/21 - 3.3.07

Application Number: 11805824.7

Publication Number: 2651398

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Language of the proceedings: EN

Title of invention:
SOLID COMPOSITIONS COMPRISING A GLP-1 AGONIST AND A SALT OF N-(8-(2-HYDROXYBENZOYL)AMINO)CAPRYLIC ACID

Patent Proprietor:
Novo Nordisk A/S

Opponents:

Generics (U.K.) Limited
Hexal AG
Galenicum Health S.L.U.

Headword:
Solid compositions of a GLP-1 agonist / NOVO NORDISK

Relevant legal provisions:
EPC Art. 100(b), 83, 100(a), 56

Keyword:
Grounds for opposition - insufficiency of disclosure (no) - lack of inventive step (no)

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Case Number: T 1404/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 26 June 2024

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Decision under appeal:

Decision of the Opposition Division of the European Patent Office posted on 29 July 2021 rejecting the opposition filed against European patent No. 2651398 pursuant to Article 101(2) EPC.

Composition of the Board:

Chairwoman Y. Podbielski
Members: J. Lécaillon
D. Boulois

Summary of Facts and Submissions

I. European patent 2 651 398 (hereinafter "the patent") was granted on the basis of 13 claims. The claims of the patent as granted relevant for the present decision read as follows:

"1. A solid composition for oral administration comprising a GLP-1 agonist and a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid,
wherein the amount of said salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid is at least 0.6 mmol; and wherein said GLP-1 agonist is semaglutide."

"12. A composition as defined in any one of the preceding claims for use in medicine."

"13. A composition according to claim 12, for use in the treatment of type II diabetes or obesity."

II. Four oppositions were filed against the patent on the ground that its subject-matter lacked an inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as originally filed.

III. The opposition division took the decision to reject the oppositions.

IV. The decision of the opposition division, posted on 29 July 2021, cited *inter alia* the following documents:

D1: C. Beglinger *et al.*, Clinical Pharmacology & Therapeutics 84(4), 468-474 (2008)
D2: WO 2010/020978 A1

D4: WO 2006/097537 A2
D5: JP 4585037 B = JP2010116407, family member of D4
D5a: English translation of claims of D5
D9: M. Kidron *et al.*, Diabetic Medicine 21 (4), 354-357 (2004)
D10: US 2008/0194676 A1
D16: Drug Data Report 28(10), 933 (2006)
D17: C.M. Keck *et al.*, "Moderne Pharmazeutische Technologie - Lehrbuch für Studierende", 2009, Kapitel 1.2, H. E. Junginger, "Delivery Systeme für die perorale Applikation van Peptiden", p. 8-14
D18: R.E. Steinert *et al.*, Clinical Pharmacology & Therapeutics 86(6), 644-650 (2009)
D21: R.E. Steinert *et al.*, Am. J. Clin. Nutr. 92, 810-817 (2010)
D22: Declaration by the inventor, Flemming S. Nielsen, 11.02.2019
D24: M. Davies *et al.*, JAMA 318(15), 1460-1470 (2017) and supplementary materials
D30: E.T. Hellriegel *et al.*, Clinical Pharmacology & Therapeutics 60(6), 601-607 (1996)
D31: S.T. Buckley *et al.*, Sci. Transl. Med. 10, eaar7047, 1-13 (2018) including supplementary materials
D36: M. Christensen *et al.*, Curr. Diab. Rep., 10, 124-132 (2010)
D40: A. Bhansali et al., Suppl. to JAPI, Vol. 58, pages 10-14, June 2010

V. The opposition division came *inter alia* to the conclusions that the patent as granted met the requirements of Article 83 EPC and that the subject-matter of granted claim 1 involved an inventive step starting from D1 as well as from D4/D5 as closest prior art document.

VI. Opponents 1, 2 and 3 (appellants) lodged appeals against the above decision of the opposition division.

VII. With its reply to the appellants' statements setting out the grounds of appeal the patent proprietor (respondent) defended its case on the basis of the patent as granted as the main request, and on the basis of auxiliary requests 1 to 14 filed therewith and corresponding to auxiliary requests 1 to 12, 3A and 7A filed during the first instance proceedings.

VIII. With the letter dated 9 January 2024, appellant - opponent 1 withdrew its opposition and was consequently no longer party to the proceedings.

IX. The following item of evidence was filed by appellant - opponent 3 with its statement setting out the grounds of appeal:

D51: Letter of Novo Nordisk A/S dated 3 July 2008 filed in the examination proceedings for European patent application EP 06 725 149.6

X. Oral proceedings were held before the Board on 26 June 2024.

XI. As indicated with the letter dated 6 May 2024, opponent 4 (party as of right) did not attend the oral proceedings. They did not make any substantial submission in the appeal proceedings.

XII. The appellants (opponents 2 and 3) requested that the decision under appeal be set aside and that the patent be revoked.

XIII. The respondent requested that the appeals be dismissed, *i.e.* that the patent be maintained as granted (main request), or, if the decision under appeal was set aside, that the patent be maintained on the basis of one of the auxiliary requests 1 to 14 submitted with the reply to the statements setting out the grounds of appeal.

XIV. The arguments of the appellants, as far as relevant for the present decision, can be summarised as follows:

(a) According to appellant - opponent 3, the subject-matter of claims 12 and 13 was not sufficiently disclosed. The suitability for the use in the claimed treatment had not been established. In view of the low bioavailability of semaglutide, it was not plausible that an orally administered solid composition thereof would be therapeutically effective and the data provided in the patent did not demonstrate it either, in particular not in human subjects. Furthermore, the quality of the data provided in the patent was questionable.

(b) D1 as well as D4/D5 represented suitable starting points for the assessment of inventive step.

Starting from D1 as closest prior art, the claimed composition differed from the one disclosed therein in the nature of the active ingredient (semaglutide instead of GLP-1 in D1). No technical effect had been demonstrated for this distinguishing feature compared to the closest prior art. Indeed no comparative examples had been performed and the results of the patent, D1 and D31 could not be compared since the performed experiments differed from each other in the amounts of ingredients and

in the nature of the subjects used. The objective technical problem resided therefore in the provision of a solid pharmaceutical composition suitable for oral administration of an alternative GLP-1 analogue. D18, a follow-up study of D1, suggested to replace GLP-1 with a long-acting analogue thereof. Semaglutide was a well-known long-acting GLP-1 analogue (see *e.g.* D40 or D16) and represented at least an equal alternative to other known long-acting analogues such as exenatide or liraglutide. The skilled person would thus have replaced GLP-1 in the composition of D1 by semaglutide. Moreover, the skilled person would have had a reasonable expectation of success of achieving acceptable bioavailabilty upon oral administration of such a composition, because SNAC was generally described as an absorption enhancer which could be used with a range of various active macromolecules (see *e.g.* D1, D2, D9, D10, D17, D18 and D40).

Starting from D4/D5 as closest prior art, the claimed composition differed from the one disclosed therein in that it contained at least 0.6 mmol of a salt of NAC. D4/D5 actually disclosed a solid composition suitable for oral administration (see page 33 lines 1 to 14). However, for the sake of the argument, it was also considered that the claimed composition differed from the specific one exemplified in D4 (see page 63) in that it was a solid composition. No technical effect had been experimentally demonstrated for these distinguishing features compared to the closest prior art. Avoidance of needle-phobia was however to be taken into consideration for the sake of argumentation. The objective technical problem as

formulated during oral proceedings resided in the provision of a pharmaceutical composition of semaglutide suitable for administration without the use of needles. D4 addressed the issue of needle-phobia and generally disclosed tablets and capsules as possible formulations, thus rendering the provision of an oral solid composition obvious. Furthermore SNAC was generally known as a delivery agent for peptides having low bioavailability (see D17 and D18), including in particular for GLP-1 (see D1). It would therefore have been obvious to formulate semaglutide with SNAC to prepare such an oral solid composition. The mimimal amount of SNAC defined in the claim would furthermore be arbitrarily defined and could thus not provide inventiveness.

Hence, the granted patent did not meet the requirements of Article 56 EPC.

XV. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) The subject-matter of claims 12 and 13 was sufficiently disclosed. The suitability of semaglutide in medicine, in particular in the treatment of type II diabetes or obesity, was known from the prior art at the priority date. The suitability of the claimed solid compositions to effectively deliver semaglutide to the plasma upon oral administration in a beagle dog model was furthermore demonstrated in the examples of the patent. This rendered the achievement of acceptable bioavailability of the claimed compositions in human subjects plausible.

(b) D1 represented the closest prior art document. D4/D5 was not an appropriate choice as closest prior art since it did not relate to the oral administration of semaglutide, which was the key purpose of the patent, and has less features in common with the present invention than D1.

Starting from D1 as closest prior art, the objective technical problem resided in the provision of an oral formulation having a more protracted GLP-1 effect *in vivo*. The pharmacokinetic data provided in the patent, D31 and D1 did substantiate that this problem had been solved by the claimed composition. In this context, the effect shown in the post-published document D31 could be taken into account according to G 2/21, since it merely confirmed an effect already considered in the patent. Starting from D1, the skilled person willing to achieve a protracted effect *in vivo* would have considered many different options, using a long-acting GLP-1 analogue being merely one of them. Even if the skilled person would have considered replacing GLP-1 by a long-acting analogue, well-characterised GLP-1 analogues such as liraglutide or exenatide (see *inter alia* D21, D36) would have been preferred to semaglutide. Finally the skilled person would not have applied the SNAC containing formulation of D1 to semaglutide with a reasonable expectation of success to achieve acceptable bioavailability upon oral administration.

D4/D5 did not disclose a solid oral composition of semaglutide. Starting from D4/D5 as closest prior art, the objective technical problem resided in the provision of an improved way to administer

semaglutide in order to avoid the problems of "needle-phobia" and so improve patient compliance. D4/D5 disclosed many possible alternative administration routes, the oral route not being the most favoured one. Even if the skilled person would have considered the oral administration route, the prior art still did not provide any guidance on how to prepare an appropriate composition therefor. In particular, the cited prior art would not have provided to the skilled person any reasonable expectation of success of achieving acceptable bioavailability of semaglutide upon oral administration with SNAC.

Hence, the granted patent met the requirements of Article 56 EPC.

Reasons for the Decision

Main request - Granted patent

1. Amendments

The appellants did not pursue in the appeal stage the objection under Article 100(c) EPC. The Board agrees with the impugned decision that the ground of opposition under Article 100(c) EPC does not prejudice the maintenance of the patent.

2. Sufficiency of disclosure

2.1 Appellant - opponent 3 contested that the invention according to the medical use claims 12 and 13 of the main request was sufficiently disclosed.

2.2 The Board observes that the suitability of semaglutide *per se* to exert a therapeutic effect useful in the treatment of type II diabetes and obesity was not contested. The point of dispute was whether the claimed solid composition would allow for sufficient semaglutide to be delivered to blood circulation upon oral administration for said effect to be exerted.

2.3 The objection of appellant - opponent 3 was based on the known low bioavailability of semaglutide, which compound had at the priority date only been reported for intravenous administration. According to appellant - opponent 3, the data provided in the patent would not allow to conclude that sufficient bioavailability would be obtained upon oral administration to humans. The quality of the data would indeed be questionable and no evidence had been provided allowing to extrapolate the results to human subjects.

2.4 These arguments are not convincing.

2.5 The patent provides data on the bioavailability of semaglutide upon oral administration of compositions according to the claims to beagle dogs, see example 1, in particular Tables 2 and 7. While the C_{max} values obtained may not be as high as those obtained upon intravenous administration (higher or similar C_{max} for intravenous administration of a 100-fold lower dose of semaglutide, see Table 6), it was nevertheless the case that semaglutide was delivered to the blood of the subjects to a non negligible level. This renders the achievement of a therapeutic effect in this dog model credible. In this context the Board underlines that specific bioavailability and/or efficacy levels do not constitute any feature of the claims and hence any requirement under Article 83 EPC.

2.6 Appellant - opponent 3 argues that a great variability amongst individual subjects would be observed, which would question the quality of the experimental data provided. The Board considers that, as argued by the respondent, such a variability would be expected for *in vivo* experiments of oral administration of agents known to have a low bioavailability (see D22, items 27 to 30 with reference to D30). The mean data provided in Tables 2 and 7 do furthermore take into account this variability and are considered meaningful.

2.7 Finally, regarding the lack of data in human subjects, the Board notes that, in the absence of any indication to the contrary (*e.g.* due to different mechanisms of adsorption in dogs and humans), there appears to be no reason to consider that the achievement of acceptable bioavailability in a commonly used beagle dogs model would not also occur to some extent in human subjects. According to established Case Law, clinical trials in human subjects are not necessarily required to substantiate the achievement of a therapeutic effect (see T 609/02 point 9. of the reasons and T 241/95 point 4.1.2 of the reasons).

2.8 Hence, in the absence of serious doubts substantiated by verifiable facts, that the claimed therapeutic use cannot be achieved by oral administration of the claimed compositions, the Board is of the opinion that the main request meets the requirements of Article 83 EPC.

2.9 Accordingly the ground of opposition under Article 100(b) EPC does not prejudice the maintenance of the patent.

3. Inventive step

3.1 Closest prior art

3.1.1 The patent relates to a solid oral composition of semaglutide containing at least 0.6 mmol of a salt of NAC for use in the treatment of type II diabetes or obesity (see *e.g.* paragraphs [0004] and [0065]). The low bioavailability of GLP-1 and its analogues upon oral administration are discussed in paragraph [0002]. According to paragraph [0005] of the patent, the claimed oral compositions provide improved exposure and/or bioavailability of the GLP-1 agonist.

3.1.2 The parties disagreed on the choice of the closest prior art. The appellants, in line with the decision of the opposition division, considered both D1 and D4/D5 as suitable starting points for the assessment of inventive step. The respondent considered that D1 represented the only suitable starting point as it was relatively closer to the invention than D4/D5.

3.1.3 In this context, as argued by the appellants, it is established case law that the claimed subject-matter must be non-obvious having regard to any prior art(Case Law of the Boards of Appeal, 10th Edition, 2022, I.D. 3.1, page 191, 2nd full paragraph). If several documents constitute realistic starting points, then the claimed subject-matter must be inventive over all of them for an inventive step to be acknowledged.

3.1.4 D1 relates to the treatment of type II diabetes and/or obesity. It reports the successful oral administration of tablets containing GLP-1 and SNAC as delivery agent (in an amount of 200 mg *i.e.* around 0.66 mmol, hence above 0.6 mmol) to overcome the issue of low

bioavailability of GLP-1 (see page 473, left column,"Study design"; page 473, right column, "Materials"; Table 1). Hence it relates to a similar purpose as the present invention. However, semaglutide is not mentioned in D1.

3.1.5 D4 and the Japanese family member D5 also relate to the treatment of *inter alia* type II diabetes and/or obesity. D4/D5 concern new GLP-1 analogues which can be administered less than once daily while retaining an acceptable clinical profile to reduce "needle-phobia" in patients (see D4, page 1 lines 26-33). The analogues are said to have extended plasma half-lives and to be suitable for once weekly administration (see page 59 line 24-26). Semaglutide is disclosed in example 4 of D4/D5 and individualised in the claims of D5. The sole exemplified composition is a liquid pharmaceutical composition comprising semaglutide (see page 63 lines 10 to 15). As underlined by the appellants, D4/D5 generally describe a wide range of possible dosage forms including solid ones as well as a wide range of possible administration routes including the oral route (see D4, page 33 lines 1 to 14). Also the compounding in a drug carrier or drug delivery system is very generally described (see page 33 lines 15 to 30 of D4). However D4/D5 do not provide any specific disclosure of a solid oral composition containing semaglutide and appear to focus for the PK/PD study on subcutaneous and intravenous administration. Moreover, D4 does not disclose the use of a salt of NAC, let alone in the presently claimed amount.

3.1.6 Thus, D1 focuses on oral administration of the naturally occurring GLP-1 but does not mention semaglutide. On the other hand D4/D5 concern pharmaceutical compositions of semaglutide but the

examples are limited to liquid compositions and parenteral administration routes. In the present case, contrary to the opinion of the respondent, it is not appropriate to give more weight to the disclosed purpose of the oral administration (D1) over the disclosure of injectable formulations containing specifically semaglutide (D4/D5). The Board considers therefore that D1 and D4/D5 represent two equally suitable starting points for the assessment of inventive step.

3.2 Problem solution approach starting from D1

Distinguishing feature

3.2.1 It was undisputed amongst the parties that the subject-matter of present claim 1 differed from the one disclosed in D1 in that GLP-1 had been replaced by its analogue semaglutide.

Technical effect and objective technical problem

3.2.2 The respondent argued that the claimed formulations containing semaglutide would have a more protracted GLP-1 effect *in vivo* compared to formulations containing GLP-1 according to D1.

3.2.3 The Board observes that, as argued by the appellants, no comparative experiments between oral administration of the GLP-1 compositions of D1 and semaglutide compositions according to the present claims have been provided. The respondent based its reasoning *inter alia* on the difference in half-lives between GLP-1 and semaglutide as well as the plasma profiles of GLP-1 and semaglutide after oral administration as disclosed in D1 (GLP-1), the patent as well as D31 (semaglutide).

3.2.4 The patent provides in the examples detailed pharmacokinetic parameters following the oral administration of compositions according to the invention in a beagle dogs model (see Tables 4, 5 and 7 to 10). As argued by the respondent during oral proceedings, the mean T_{max} may reach up to more than an hour and the mean AUCinf./D, which would provide an indication of the total amount of exposure to the active ingredient, is rather high (see for example composition B in Table 4 having a mean AUCinf./D of 2.35 which would correspond to around 620 000 pmol exposure). According to the respondent, this substantiates that semaglutide remains in the plasma for an extended period of time.

3.2.5 This conclusion is confirmed by the plasma profiles provided in D31, a post-published scientific article. As explained by the respondent during oral proceedings, the plasma profile of semaglutide after oral administration of a composition comprising 10 mg semaglutide and 300 mg SNAC to beagle dogs is reported in Figure 1B (see page 2, left-hand column, 1st paragraph under the heading "Results", 2nd sentence). The T_{max} and AUC data are in line with those reported in the patent (see 3.2.4). Furthermore it can be observed that the semaglutide plasma levels remain high for at least the 24 hours duration of the measure (see Figure 1B and page 2, left-hand column, 1st paragraph under the heading "Results", 5th sentence).

In this context, the fact that the data provided in D31 could be taken into account to support a technical effect in the context of the inventive step discussion has not been disputed by the appellants. The Board considers that the data of D31 referred to by the

respondent in the present context merely further confirm the data already provided in the patent. The Board is therefore satisfied that the skilled person would derive the effect supported by D31 as being encompassed by the technical teaching and embodied by the same originally disclosed invention.

3.2.6 As underlined by the respondent, this plasma profile following oral administration of semaglutide and SNAC is in striking contrast with the one following oral administration of compositions comprising GLP-1 and SNAC described in D1 (see Figure 1(a)) which shows a high mean peak but a rapid elimination of GLP-1 reaching the zero level after at most 1 hour. These results are in line with the reported extended half-life of semaglutide compared to GLP-1 (see D4, D16).

3.2.7 The appellants explained that the experiments of D1 and D31 were performed on different subjects (humans in D1; beagle dogs in D31) and using different drug amounts, so that no fair comparison could be done.

However, the beagle dog model used in D31 is a commonly recognised animal model. Moreover, as emphasised by the respondent, later phase II clinical trials reported in D24 confirm the effectiveness as GLP-1 analogue of semaglutide orally administered with SNAC in humans. In the absence of any evidence that the metabolism of beagle dogs and of humans would be so different that the overall plasma levels profiles would be significantly modified from one specie to the other for each active ingredient, the argument of the appellants is not convincing.

Regarding the difference in amounts administered, the Board considers that the overall profile of plasma

levels is expected to remain the same, albeit at different absolute levels depending on the administered amounts.

3.2.8 As a result, while no direct comparison was performed, it remains the case that the overall plasma levels profiles of both active ingredients administered orally with SNAC render credible that semaglutide will remain for a significant longer time period in the plasma compared to GLP-1. Furthermore D31 indicates that the achieved plasma exposure of semaglutide is therapeutically relevant (see page 8, left-hand column, 1st paragraph under the heading "Discussion", 2nd sentence). Hence the Board considers it credible that orally administered semaglutide formulations according to the main request will provide a more protracted effect *in vivo* compared to orally administered GLP-1 formulations of D1.

3.2.9 The objective technical problem starting from D1 can therefore be formulated in line with the respondent as the provision of an oral solid pharmaceutical composition for use in the treatment of type II diabetes or obesity having a more protracted GLP-1 effect *in vivo*.

3.2.10 Appellant - opponent 2 contested the inclusion of the therapeutic application in the formulation of the problem because independent claim 1 would not be a medical use claim and the technical effect could not be acknowledged. The Board disagrees. First of all the suitability of the claimed composition in the treatment of type II diabetes or obesity is considered to be established (see above 2.2 to 2.8). This therapeutic application is furthermore defined in the patent as the purpose of the invention (see paragraphs [0054] and

[0065]). It may thus be taken into account in the formulation of the objective technical problem even for claims to the composition *per se*. Moreover, for the reasons detailed above (see 3.2.2 to 3.2.8), also the particular technical effect included in the above objective technical problem is considered to have been credibly demonstrated. Its inclusion in the objective technical problem is therefore justified.

Obviousness of the solution

3.2.11 The Board considers that the skilled person willing to solve the problem posed, *i.e.* to provide a protracted GLP-1 effect *in vivo*, would have considered obvious to replace GLP-1 by one of its known long-acting analogues. Moreover, all parties considered that the skilled person would have consulted D18, which is a follow-up study of D1. D18 suggests to replace GLP-1 by a long-acting analogue thereof without any particular pointer to a specific one (sentence bridging both columns on page 648).

3.2.12 Semaglutide was known at the priority date as being a long-acting analogue of GLP-1 (see D4, D16 and D40).

3.2.13 Contrary to the respondent's view, the skilled person would not necessarily have preferred "well-characterised, licensed or late clinical stage analogues" such as exenatide or liraglutide over other known analogues. In particular, the isolated mention in D21 - another follow-up study of D1 - of exenatide and liraglutide as examples of such long-acting analogues (see page 816, paragraph bridging both columns) does not represent a clear pointer towards these analogues over any other one. Since semaglutide was described as suitable for a once weekly administration (see *e.g.* D40

page 13), the skilled person would have understood that it had even extended half-life compared to liraglutide (half-life of 13 hours after subcutaneous administration, see D36, page 126, left-hand column, 1st paragraph)) or exenatide (half-life of around 2 hours after subcutaneous administration, see D36, page 125, right-hand column, 2nd full paragraph under the heading "Exenatide") which were described to be administered daily (see *e.g.* D40, page 12).

3.2.14 Hence, the Board considers that semaglutide constituted one of equally disclosed GLP-1 long-acting analogues available to the skilled person.

3.2.15 Nevertheless, semaglutide was known at the priority date as having a poor bioavailability upon oral administration, for which reason it had only been administered by injection. It remains therefore to be determined whether the skilled person would have expected the SNAC containing formulation disclosed in D1 to work with semaglutide, *i.e.* to achieve delivery of semaglutide to plasma upon oral administration.

3.2.16 The appellants argued that SNAC was generally known as a delivery agent for active ingredients having a low bioavailability. According to the appellants, the knowledge on SNAC at the priority date (see description of the corresponding technology in D1, page 473, right column, under "Materials" and in D18, page 644, right-hand column, sentence starting from 6th line from the bottom; list of macromolecules to which the Eligen® technology was applied in D17, Table on page 9 and combination with various drugs in D2, D9, D40 and D10; description of the mechanism of drug delivery by SNAC in D17 Figure 1 and last sentence on page 8, in D1, page 472, left-hand column and in D18, page 644, right-

hand column) would have been such as to provide the skilled person with a reasonable expectation of success of achieving also an acceptable bioavailability when replacing GLP-1 with other analogues including semaglutide.

3.2.17 The Board observes that it is commonly accepted that a specific effect obtained for a given excipient with a given active ingredient cannot be extrapolated to another active ingredient. Thus the successful delivery of GLP-1 to plasma achieved with SNAC in D1 cannot *per se* be generalised to semaglutide.

3.2.18 There is furthermore no clear indication in any of the cited prior art, that SNAC would indeed successfully deliver GLP-1 analogues, let alone specifically semaglutide. The fact that successful delivery of diverse macromolecules was achieved with SNAC does not appear sufficient to provide a reasonable expectation of success in the case of semaglutide. As explained by the respondent, given the mechanism by which SNAC increases the delivery of an active ingredient to the plasma, namely by formation of a complex with the active ingredient (see D17 Figure 1 and last sentence on page 8; D1, page 472, left-hand column; D18, page 644, right-hand column), the skilled person would have been aware that the structural differences between semaglutide and GLP-1, in particular the presence of a side chain on the Lysine at position 26 of semaglutide, may influence the interaction with SNAC and thus the effectiveness of the delivery.

3.2.19 Furthermore, contrary to the opinion of the appellants expressed during oral proceedings, it cannot be considered obvious for the skilled person to test all possible GLP-1 long-acting analogues in a simple try

and see strategy. The required testing would involve *in vivo* clinical trials and reach far beyond routine testing.

3.2.20 Hence the Board considers that the skilled person would not have had any reasonable expectation of success to solve the problem posed by replacing GLP-1 with semaglutide in the formulation of D1. Only an *ex-post facto* analysis going beyond what the skilled person would have objectively inferred from the prior art could lead to an opposite conclusion.

3.3 Problem solution approach starting from D4/D5

Distinguishing feature

3.3.1 As detailed above (see 3.1.5), the sole specific semaglutide composition disclosed in D4/D5 is a liquid formulation (see page 63 lines 10 to 15). Contrary to the appellants' opinion, D4 does not directly and unambiguously disclose a solid oral composition containing semaglutide.

3.3.2 Accordingly, the subject-matter of present claim 1 differs from the specific formulation disclosed D4/D5 at least in that the composition is solid and contains at least 0.6 mmol of a salt of NAC.

Technical effect and objective technical problem

3.3.3 The respondent argued that the presence of NAC in the claimed amount had the effect of providing improved bioavailability to the claimed compositions upon oral administration.

3.3.4 The Board observes that no direct comparison with any other formulation has been provided.

3.3.5 The respondent argued that, in view of the commonly known poor bioavailability of semaglutide, the level of semaglutide in the plasma following oral administration of a solid composition without a salt of NAC would be negligeable and referred to data mentioned in paragraph 58 of D22 regarding administration of semaglutide without absorption enhancer. However, this argument merely supports the suitability of the claimed solid composition to deliver semaglutide to the plasma upon oral administration.

3.3.6 It nevertheless remains that no comparison of the bioavailability following oral administration of the claimed compositions and following subcutaneous or intravenous administration of the closest prior art liquid composition of D4 according to the examples thereof has been provided. No improvement compared to the closest prior art in terms of bioavailability can thus be taken into account.

3.3.7 In this context, the Board notes that also no particular effect linked to the claimed minimal amount of NAC salt has been demonstrated. In particular lower amounts of SNAC also provide acceptable (even if lower) bioavailability (see composition A compared to compositions B to F in Tables 2 and 7).

3.3.8 During the oral proceedings, it was undisputed that the suitability for oral administration avoids the problems of "needle-phobia" mentioned in D4/D5 (see page 1).

3.3.9 Hence, the objective technical problem starting from D4/D5 resides in the provision of a pharmaceutical

composition of semaglutide for use in the treatment of type II diabetes or obesity through administration by an alternative route avoiding needle-phobia.

3.3.10 In this context the same comments regarding the inclusion in the objective technical problem of the therapeutic application as developed above (see 3.2.10) apply *mutatis mutandis*.

Obviousness of the solution

3.3.11 The appellants considered that D4 itself rendered the provision of an oral solid composition obvious, since it generally disclosed tablets and capsules as possible formulations as well as formulations further containing drug delivery systems enhancing bioavailability (see page 33 lines 7 to 20) and also addressed the issue of needle-phobia (see page 1 lines 27 to 28). Furthermore, as discussed in the context of the problem solution approach starting from D1, SNAC was generally known as a delivery agent for peptides having low bioavailability (see D17 and D18), including in particular for GLP-1 (see D1). According to the appellants, it would therefore have been obvious to formulate semaglutide with SNAC to prepare such an oral solid composition.

3.3.12 The Board agrees that the choice of an oral administration route *per se* to avoid needle-phobia is generally an obvious one. However, the prior art provides no indication that semaglutide could be successfully orally administered when formulated with SNAC. For the same reasons as detailed above starting from D1 (see 3.2.15 to 3.2.19), the Board considers that the skilled person would not have had any reasonable expectation of success to achieve acceptable

results with oral administration of the known poorly bioavailable semaglutide when formulating it with SNAC. Only an *ex-post facto* analysis going beyond what the skilled person would have objectively inferred from the prior art could lead to the opposite conclusion.

3.4 Conclusion on inventive step

As a result, the ground of opposition under Article 100(a) EPC in combination with Article 56 EPC does not prejudice the maintenance of the patent.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairwoman:

B. Atienza Vivancos Y. Podbielski

Decision electronically authenticated