Internal distribution code:

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

Datasheet for the decision of 13 September 2024

Case Number: T 0291/22 - 3.3.04

Application Number: 13709231.8

Publication Number: 2827885

IPC: A61K38/26, A61P3/10, A61K47/00

Language of the proceedings: EN

Title of invention:
Compositions of GLP-1 peptides and preparation thereof

Patent Proprietor:
Novo Nordisk A/S

Opponents:
Teva Pharmaceutical Industries Ltd.
Galenicum Health S.L.U.
Hexal AG
Generics (U.K.) Limited

Headword:
GLP-1 compositions/NOVO NORDISK

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

Keyword:
Inventive step - (no)

Decisions cited:
T 0041/16, T 0640/91, G 0007/93

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 0291/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 13 September 2024

Appellant: (Patent Proprietor)	Novo Nordisk A/S Novo Allé 2880 Bagsværd (DK)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
Respondent I: (Opponent 1)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	von Kauffmann, Carl Global IP Group - Teva Graf-Arco-Straße 3 89079 Ulm (DE)
Respondent II: (Opponent 2)	Galenicum Health S.L.U. CL Sant Gabriel n°50 08950 Esplugues de Llobregat (ES)
Representative:	Torrejón-Nieto, Javier Galenicum Health S.L.U. CL Sant Gabriel n°50 08950 Esplugues de Llobregat (ES)
Respondent III: (Opponent 3)	Hexal AG Industriestraße 25 83607 Holzkirchen (DE)
Representative:	Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)

Respondent IV: (Opponent 4)	Generics (U.K.) Limited Building 4, Trident Place Mosquito Way Hatfield Herts AL 10 9UL (GB)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 7 December 2021 revoking European patent No. 2 827 885 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	B. Rutz
	L. Bühler

Summary of Facts and Submissions

I. The appeal by the patent proprietor (appellant) lies from the decision of the opposition division to revoke European patent No. 2 827 885, which is based on European patent application No. 13 709 231.8, published under the PCT as international application WO 2013/139694.

II. The patent had been opposed on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and Article 100(b) and (c) EPC.

III. With regard to the main request (patent as granted), the opposition division decided *inter alia* that the subject-matter of claim 1 did not involve an inventive step over the disclosure of document D2 combined with that of any one of documents D17, D20, D24, D25, D29, D30 and D31 (Article 56 EPC).

Essentially the same arguments applied to claim 1 of auxiliary requests 1, 2, 2A (former auxiliary request 12), 3, 4, 5, 5A, 6 to 11 and 13.

IV. With its statement of grounds of appeal, the appellant filed sets of claims of a main request and of auxiliary requests 1 to 15. The main request and auxiliary requests 1 to 12 are identical to auxiliary requests 1, 2A, 3, 4, 5, 5A, 6 to 11 and 13, respectively, dealt with in the decision under appeal. Auxiliary requests 13 to 15 were newly filed with the statement of grounds of appeal.

V. Opponents 1 to 4 (respondents I to IV, respectively) replied to the appeal.

VI. By letter dated 14 December 2022 the appellant submitted a corrected version of the set of claims of auxiliary request 14 wherein in claim 1 "a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid" had been added after "at least 75 % (w/w)".

VII. By letter dated 11 March 2024 the appellant filed sets of claims of an amended auxiliary request 1 in which the erroneous deletion of "wherein" in claim 2 had been corrected, and sets of claims of new auxiliary requests 16 and 17.

VIII. The board summoned the parties to oral proceedings and informed them of its preliminary opinion in a communication under Article 15(1) RPBA.

IX. Oral proceedings were held in the absence of respondent II as announced in its letter dated 24 May 2024. As per Rule 115(2) EPC and Article 15(3) RPBA, respondent II was treated as relying on its written submissions. During oral proceedings the appellant withdrew all its requests except for the main request and auxiliary requests 1 and 5.

X. Claim 1 of the main request reads as follows:

"1. A pharmaceutical composition comprising a first type of granules and a second type of granules, wherein said first type of granules comprises a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid and no GLP-1 peptide, and

wherein said second type of granules comprises a GLP-1 peptide and no salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid, and
wherein said composition is in the form of a solid dosage form selected from the group consisting of a tablet, a capsule, and a sachet."

Claim 1 of auxiliary request 1 contains the following additional wording at the end:

", and wherein the release of said salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid is faster than the release of said GLP-1 peptide as determined by dissolution testing using Assay (I) at pH 2.5, as described herein."

Claim 1 of auxiliary request 5 reads as follows:

"1. A pharmaceutical composition consisting of a first type of granules, a second type of granules and an extragranular part,
wherein said first type of granules comprises at least 75 % (w/w) of a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid, less than 10 % (w/w) lubricant, optionally less than 20 % (w/w) filler and no GLP-1 peptide, and
wherein said second type of granules comprises a GLP-1 peptide, a binder and a filler, wherein said second type of granules comprises at least 15 % (w/w) filler, less than 40 % (w/w) binder and no salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid,
wherein the extragranular part consists of a lubricant,
wherein the composition comprises at least 60 % (w/w) the salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid, and

wherein said composition is in the form of a solid dosage form selected from the group consisting of a tablet, a capsule, and a sachet."

XI. At the end of the oral proceedings in the presence of the appellant and respondents I, III and IV, the chairwoman announced the board's decision.

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

D2 WO 2012/080471 A1

D11 B. J. Aungst, "*Absorption Enhancers: Applications and Advances*", The AAPS Journal 14(1), 2012, 10-18

D16 Granulation, eds. A. D. Salman, M. J. Hounslow, J. P. K. Seville, Handbook of Powder Technology 11, 2006, 1190

D17 Handbook of Pharmaceutical Granulation Technology, ed. D. M. Parikh, Drugs and the pharmaceutical sciences 198, 2010, 7, 10-14, 330

D18 Pharmaceutical process engineering, eds. A. J. Hickey and D. Ganderton, Drugs and the pharmaceutical sciences 195, 2010, 159

D20 WO 2006/124047 A2

D24 WO 2011/094531 A1

D25 WO 2007/146234 A2

D29 WO 2005/107462 A2

D30 WO 2006/084164 A2

D31 WO 2008/003050 A2

D36 Declaration by Dr Peter Rue, 4 pages

D37 S. Abdul et al., "*A flexible technology for modified-release drugs: Multiple-unit pellet system (MUPS)*", Journal of Controlled Release 147, 2010, 2-16

D38 Declaration by T. Vilhelmsen, 2 pages

D40 Graphs depicting the data of Tables 4 to 8, 10 and 11 of the patent in suit at pH 2.5

XIII. The appellant's submissions are summarised as follows:

Main request
Inventive step (Article 56 EPC)

Document D2 provided a detailed description of how a glucagon-like peptide 1 (GLP-1) agonist (e.g. the GLP-1 peptide semaglutide) and a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid (NAC; SNAC being the sodium salt) were formulated in a tablet composition (see page 26). The difference defined by the claims was the separation of the GLP-1 peptide and a salt of NAC into different granules. The two-granule system of the invention provided improved dissolution characteristics and improved bioavailability, as evident from the comparison with composition D, which comprised a single granule (see Table 3 in the patent) and was very similar to Tablet B as disclosed in document D2 (see Table 1 therein).

The graphs in document D40, depicting the data of Tables 4 to 8, 10 and 11 of the patent in suit at pH 2.5, showed that the dissolution of semaglutide and SNAC from tablets with semaglutide and SNAC in separate granules was markedly and consistently different from tablets with a single type of granules comprising both semaglutide and SNAC. In particular, at pH 2.5, SNAC was released at a faster rate than semaglutide from each of the tablets using the two-granule system – Tablets B, F, G and H. In contrast, each of the tablets with a single type of granules – Tablets C, D (which was very similar to Tablet B in D2) and E - released

semaglutide at a faster rate, or released semaglutide and SNAC at the same rate. Tablet B and Tablet F both used the two-granule system and both exhibited the same dissolution profile, despite having a different distribution of microcrystalline cellulose. The same effects, although less pronounced, were observed at pH 1.0. Therefore separating semaglutide and SNAC into different granules resulted in consistent changes to dissolution characteristics.

Different tablet compositions had been tested and each tablet composition had the same overall amount of SNAC, semaglutide, magnesium stearate, microcrystalline cellulose and povidone. Using the same excipients in the same amounts in the compositions tested allowed the dissolution and bioavailability of the compositions to be compared.

It was impossible to generate a composition comprising a single type of granules and a composition comprising two granules that differed only in the separation of the NAC salt and the GLP-1 peptide. If the GLP-1 peptide was removed from the first granule and incorporated into a second granule that was identical except for the absence of the NAC salt, then the composition as a whole would be much larger and the NAC salt and GLP-1 peptide would be present in the composition as a whole at a much lower concentration than in the single-granule composition. Alternatively, if the total amounts of all the ingredients in the composition were kept constant and two identical granules were generated, then the NAC salt and GLP-1 peptide would be present in their respective granules at a higher concentration than in the single-granule composition. A similar scenario was addressed in decision T 41/16 (see points 3.2.4 of the Reasons).

Neither the opposition division nor any of the opponents had shown that any excipient had such a profound and consistent effect in the examples of the patent that the effect reported for the two-granule system might not be real. Even if one or more of the excipients also influenced dissolution and bioavailability, it was not credible that the improvements reported in the patent were incorrectly attributed to separation of SNAC and semaglutide into different granules.

The bioavailability of tablet compositions B to F following oral administration to dogs was tested in Example 7 (see results in Table 9). Both compositions using the two-granule system of the invention exhibited higher bioavailability (B: 0.7% and F: 1%) than the three compositions using a single granule (C, D, E: 0.3 to 0.5%).

The problem addressed by the invention was to provide an improved oral pharmaceutical composition comprising a NAC salt and a GLP-1 peptide for the treatment of diabetes or obesity.

None of the prior-art documents would have prompted the skilled person to separate the GLP-1 peptide and the salt of NAC into different granules when attempting to provide improved dissolution characteristics and bioavailability. Nor would any of the prior-art documents have given the skilled person a reasonable expectation of success in achieving improved dissolution characteristics and bioavailability with two granules.

Auxiliary request 1
Inventive step (Article 56 EPC)

In addition to the technical features of claim 1 of the main request, claim 1 of auxiliary request 1 required that the salt of NAC be released from the claimed compositions faster than the GLP-1 peptide, which provided the advantageous dissolution characteristics that were reported in the patent in Tables 4 to 8, 10 and 11 and shown as graphs in document D40. The release was measured according to Assay (I) (see paragraph [0100] of the patent), which provided an output of relative amounts (% release), in order to be comparable. A "faster" release had to be from time zero, i.e. during the initial dissolution: later time points were not relevant (see also declaration D36, page 28 and declaration D38, page 6). The dissolution characteristics defined in claim 1 were shown in Table 9 of the patent to provide improved bioavailability. When the salt of NAC was released faster, more of it was available to enhance absorption of the GLP-1 peptide when it was released. None of the prior-art documents suggested using a two-granule system to achieve better bioavailability of a GLP-1 peptide.

Auxiliary request 5
Admission (Article 12(2) and (3) RPBA)

The opposition division had used its discretion to admit auxiliary request 5A (now auxiliary request 5). The present appeal proceedings were based on the requests on which the opposition division’s decision was based (Article 12(2) RPBA), so the admissibility of auxiliary request 5 could not be challenged.

Inventive step (Article 56 EPC)

Claim 1 additionally specified that the pharmaceutical composition consisted of a first type of granules, a second type of granules and an extragranular part, and that the extragranular part consisted of a lubricant. It additionally specified that the composition comprised at least 60 % (w/w) NAC salt. The claim further required the presence of particular amounts of lubricant, filler and binder in the first and second granules, distributed in accordance with the compositions tested in the patent, which the patent had demonstrated to be effective for providing improved release characteristics and bioavailability of the GLP-1 peptide. The claim also excluded the presence of any additional granules or the presence of any extragranular components other than a lubricant. The claim required a high proportion of NAC. It addressed any remaining concerns regarding the scope of the claims and inventive step.

XIV. The respondents' submissions are summarised as follows:

Main request
Inventive step (Article 56 EPC)

Document D2 represented the closest prior art. The only difference was the separation of the salt of NAC and the GLP-1 peptide into two types of granules.

The key dispute was the technical effect provided by the use of separate granules for the GLP-1 peptide and the NAC salt.

A different but arbitrary dissolution profile that did not provide any improvement in bioavailability provided no technical advantage and solved no problem.

The excipients present in each granule had an effect on the rate of release. Therefore, unless the same excipients were used in each granule, it was impossible to know whether the use of SNAC and semaglutide in separate granules or the change in the excipients resulted in the different relative rates of release. The granulation methods also had a direct effect on the properties exhibited by the final product (see e.g. document D16). The patentee had not provided examples in which the only difference was the use of SNAC and semaglutide in separate granules.

In the absence of data for individual dogs it was impossible to determine whether the data on bioavailability had any significance.

The problem therefore had to be defined as to provide an alternative pharmaceutical composition comprising an NAC salt and a GLP-1 peptide. The choice of separate granules represented one possibility which was well known in the art (see e.g. documents D17, page 330, paragraph b; D18, page 159, paragraph 2; D20, paragraphs [37], [66], claims 40, 44; D24, paragraphs [0007], [0081]; D25, paragraph [0054]; D29, paragraph [16]; D30, paragraph [249], Example 11; D31, paragraphs [109], [117]). The subject-matter of claim 1 thus lacked an inventive step.

Auxiliary request 1
Inventive step (Article 56 EPC)

The amount of SNAC was much higher than that of semaglutide in all the examples, whether of document D2 or of the patent in suit, so a relative faster release ("Release (%)") of SNAC would have no effect (see response, points 116 to 120 and figures therein). Furthermore, depending on the time chosen in the dissolution testing (e.g. 20 to 30 minutes), the rate of release of SNAC was even lower than the rate of release of semaglutide in the compositions in accordance with the claim (see reply to the statement of grounds of appeal by respondent III, points 142 to 146). Moreover, if the GLP-1 peptide was released much faster than a salt of NAC, the two could not interact (see e.g. document D11, page 15, right-hand column). If, however, the feature was interpreted as relating to absolute amounts, this would not be a distinguishing feature over the disclosure of document D2, which comprised 300 mg of SNAC and 10 mg of semaglutide, i.e. a 30-fold excess. Finally, there was no clear link between the dissolution characteristics analysed *in vitro* and the *in vivo* bioavailability data of Table 9 of the patent, in particular, with regard to any faster release of any amount of SNAC and for any period of time. The objective technical problem was thus the same as for the main request and the claimed solution was not obvious.

Auxiliary request 5
Admittance (Article 12(2) and (3) RPBA)

Claim 1 was directed to a composition comprising excipients which were not further defined. The request did not contain the same limitations as auxiliary

request 1 and hence did not comply with the requirement of convergence of auxiliary requests. The request was thus not admissible.

Inventive step (Article 56 EPC)

The difference from the closest prior-art document D2 was the same as for the main request: separation of a NAC salt and a GLP-1 peptide into different granules. Claim 2 referred to simultaneous release of the NAC salt and the GLP-1 peptide, so a "faster release" could not be a technical effect achieved over the whole scope of claim 1. The only additional limitation for the first type of granules was the presence of at least 75% SNAC because "less than 10% lubricant" included 0% lubricant and the presence of a filler was optional. The only additional limitation for the second type of granules was the presence of at least 15% filler because "less than 40% binder" also included minimal amounts of binder. These proportions solved no problem and did not imply any particular release profile. The requirement for an extragranular lubricant also did not solve any problem and did not imply any relative rate of release. The subject-matter of claim 1 did not meet the requirements of Article 56 EPC for the same reasons as the subject-matter of claim 1 of the main request.

XV. The appellant requested that the decision under appeal be set aside and the patent be maintained based on the set of claims of the main request or, alternatively, on the set of claims of either of auxiliary requests 1 or 5.

Respondents I, II, III and IV requested that the appeal be dismissed and the decision to revoke the patent be

upheld. Respondent III requested that auxiliary request 5 not be admitted into the proceedings.

Reasons for the Decision

Oral proceedings in the absence of a party duly summoned (Rule 115(2) EPC)

1. Respondent II had indicated that it would not be attending the oral proceedings, which were held in its absence. Respondent II was treated as relying only on its written case (Rule 15(3) RPBA).

Main request
Inventive step (Article 56 EPC)
Starting point and difference

2. The decision under appeal analyses inventive step starting from document D2. The parties agree on this choice. Document D2 discloses pharmaceutical compositions for oral administration (see claim 1) for the treatment of diabetes or obesity (see claim 15) which comprise a glucagon-like peptide 1 (GLP-1) agonist, preferably a GLP-1 peptide, e.g. semaglutide (see page 4, lines 13 to 16 and all the compositions of the example), and a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid (NAC; SNAC being the sodium salt) in a single type of granules.

3. Table 1 on page 26 discloses tablet composition B as:
granules consisting of:
10 mg semaglutide
300 mg SNAC
4 mg povidone
and

extragranular part consisting of:
82 mg Avicel PH 102 (microcrystalline cellulose (MCC))
4 mg magnesium (Mg) stearate

4. It is undisputed that the only difference between the claimed subject-matter and the disclosure of composition B in document D2 is the presence of a GLP-1 peptide (e.g. semaglutide) and a salt of NAC (e.g. SNAC) in separate granules.

Effect(s) and objective technical problem

5. The appellant considers that this difference caused SNAC to be released faster than semaglutide, as shown in dissolution experiments in the patent (see Examples 2 to 6 and the representation in graph form in document D40). This advantageous release profile resulted in increased, and thus improved, bioavailability of semaglutide (see Example 7 and Table 9 in the patent).

6. The respondents are of the view that the patent did not show that the formulation of a GLP-1 peptide and a salt of NAC into two separate types of granules resulted in an advantageous release profile. They are furthermore of the opinion that an advantageous release profile cannot be obtained across the whole scope of the claim, e.g. with all excipient types and distributions, with all ratios of a GLP-1 peptide to a salt of NAC and with all granulation methods. Finally, the patent did not show that the changed release profile resulted in increased bioavailability of GLP-1 peptide.

7. One crucial point to be assessed is thus whether it can be concluded from the results presented in the patent that the effect of an advantageous release profile and

a higher bioavailability of a GLP-1 peptide is credibly achieved over the whole scope of the claim.

8. If comparative tests are chosen to demonstrate inventive step on the basis of an improved effect, the nature of the comparison must be such that the alleged advantage or effect is convincingly shown to have its origin in the distinguishing feature of the claimed subject-matter compared with the starting point in the prior art (see also Case Law of the Boards of Appeal of the European Patent Office, 10th edn. 2022, I.D.4.3.2). The following criteria are relevant in this context:

(a) The comparative sample must be adequately representative of the closest prior art, and the "inventive" sample must be adequately representative of the claimed subject-matter.

(b) Since a technical effect cannot be convincingly linked to a particular feature if several features are varied in the comparative test, only one technical feature should be varied.

(c) Furthermore, it must be credible that the effect can be obtained over the entire scope claimed for it to be taken into account in determining the objective technical problem.

9. The appellant argues that composition D in the patent (see Table 3) was sufficiently similar to composition B disclosed in document D2 (see Table 1 therein) to allow for a meaningful comparison of the effects achieved by the respective differences.

10. Composition D of the patent compares to composition B of document D2 as follows:

	Composition D (patent)	**Composition B (document D2)**
Granule		
SNAC	300 mg	300 mg
semaglutide	10 mg	10 mg
povidone	8 mg	4 mg
Mg stearate	7.7 mg	-
Extragranular		
MCC	80 mg	82 mg
Mg stearate	2 mg	4 mg

11. The respondents argue that the increased amount of povidone and Mg stearate in the granule in composition D of the patent compared with composition B of document D2 provided a further effect that overlay a potential effect brought about by the separation of SNAC and semaglutide into two types of granules. Composition B in document D2 and composition D in the patent were thus not directly comparable.

12. The board, however, finds that even if it were concluded, in favour of the appellant, that these differences were so minor that they did not substantially affect the release profile of the components and the bioavailability of semaglutide, so that composition D in the patent would be adequately representative of composition B in document D2 (see criterion (a) in point 8. above), a detailed analysis of the comparative data in the assessment of inventive step leads to the conclusion that no effect can be acknowledged as resulting from the difference of the claimed subject-matter from the prior art (see points 19. to 25. below).

13. Compositions G and H, which are further embodiments of the invention, are not taken into account for the comparison with the disclosure of document D2 because they contain a different GLP-1 peptide (compound A).

14. Compositions B and F thus need to be compared with composition D as a representative of the prior art. The following table is based on Table 3 in the patent:

Tablet composition	**Composition of first type of granules (mg/tablet)**	**Composition of second type of granules (mg/tablet)**	**Extragranular ingredients (mg/tablet)**
D (similar to B in D2)	SNAC (300) semaglutide (10) povidone (8) Mg stearate (7.7)		MCC (80) Mg stearate (2)
B	SNAC (300) Mg stearate (7.7)	semaglutide (10) MCC (80) povidone (8)	Mg stearate (2)
F	SNAC (300) MCC (57) Mg stearate (7.7)	semaglutide (10) MCC (23) povidone (8)	Mg stearate (2)

15. Compositions B and F contain Mg stearate in the first type of granules together with SNAC, but not in the second type of granules, which contains semaglutide. In contrast, povidone is present only in the second type of granules, but not in the first. Furthermore, composition D contains MCC only in the extragranular part, while in compositions B and F it is present either in the semaglutide-containing granules or in both types of granules.

16. The respondents argue that the selective distribution of excipients had an effect that influenced the outcome of the comparison. Several features were varied in the comparative test, whereas only one technical feature should be varied (see criterion (b) in point 8. above). The respondents furthermore question whether an effect occurred over the whole scope of the claim, i.e. for all excipient combinations and distributions.

17. The appellant is of the view that it was not possible to devise a comparison in which only the separation of semaglutide and SNAC into separate granules was changed. Either the overall amount of excipients or the relative ratio of excipients to semaglutide or SNAC would be changed when attempting to have the same excipients in both types of granules. The comparison provided was the best possible approximation and showed the effect of the "two-granule system". The appellant in this regard also referred to decision T 41/16, which addressed a similar scenario.

18. The board does not agree. In decision T 41/16 the board stated that: "*Rather, it must be required that a composition according to the invention, which differs from a corresponding composition of the closest prior art only by the feature delimiting the claim from this prior art, exhibits the claimed improvement.*" (see Reasons, point 3.2.4, translation by the present board). A comparison wherein only the distinguishing feature was changed, i.e. one-granule type vs. two-granule type, has not been provided in the present case, so the requirement set out in decision T 41/16 is not met.

19. The further features which are changed in addition to the separation into different granule types can also

not be regarded as unsubstantial, because they have a potential effect on the result of the comparison. Povidone is a binder in the granulation process (see paragraph [0025] of the patent), but also acts as a disintegrant (or solubilising agent, see paragraphs [0026] and [0028] of the patent) when the tablet is dissolved. Mg stearate is a lubricant (see paragraph [0027]). MCC is a filler, binder and disintegrant (see paragraphs [0024] to [0026] of the patent). It was common general knowledge at the relevant date that all these excipients affect the dissolution of the granules and thus also the release profiles of ingredients in the respective granules (see document D36, points 12 to 17). This was not disputed by the parties.

20. The effect of a different distribution of excipients is also apparent from the examples in the patent. Compositions B and F and compositions G and H differ only in the distribution of MCC: either it is only present in the granules containing semaglutide (B and G) or it is split between both granule types (F and H). This difference leads to faster release of SNAC within the first 20 minutes for compositions F and H compared with compositions B and G respectively (see document D40).

21. A further example of the effect of excipients is seen when comparing compositions C and D, which are both one-granule-type compositions and differ only in the distribution of povidone. Povidone within the granule (composition D) leads to slightly slower release of both SNAC and semaglutide within the first 20 or 30 minutes compared with composition C, where povidone is present only in the extragranular part.

22. By combining SNAC with the lubricant Mg stearate in the first type of granules and semaglutide with the binder/ disintegrant povidone in the second type of granules in both compositions B and F, a bias is introduced which does not make it possible to distinguish whether the separation into different granules alone achieves an effect. In conclusion, the comparison in the patent does not credibly show an effect solely based on the separation of a GLP-1 peptide and SNAC into separate granules.

23. The board does not agree with the appellant that a different comparison would not have been possible either. It is common general knowledge in the field of galenics to set up appropriate comparative examples and controls to allow the effect of the separation into different granules to be analysed in isolation.

24. The appellant considers that the burden of proof was on the respondents to show that an advantageous dissolution profile and better bioavailability could not be achieved over the whole scope of the claim.

25. The board does not agree, because if the appellant alleges as fact that the claimed invention improves a technical effect, the burden of proof of that fact rests upon it (see also Case Law of the Boards of Appeal of the EPO, 10th edn. 2022, I.D.4.3.1). In the case at hand, moreover, the respondents, by referring to the examples in the patent, have provided evidence which supports serious doubts as to whether the effect can be achieved over the whole scope claimed. It would have been up to the appellant to dispel these doubts.

26. The inclusion of a medical use ("for the treatment of diabetes or obesity") in the objective technical

problem, as proposed by the appellant during oral proceedings, is also rejected because the claim is not limited to a particular medical use.

27. The objective technical problem is thus formulated as the provision of an alternative pharmaceutical composition comprising a salt of NAC and a GLP-1 peptide.

Obviousness

28. The skilled person aiming at an alternative pharmaceutical composition would have consulted documents disclosing general principles of granulated pharmaceutical formulations (e.g. documents D16, D17 and D18), oral dosage forms comprising a delivery agent or enhancer, such as sodium caprylate or SNAC (e.g. documents D25, D29 and D31), and in particular documents concerning pharmaceutical compositions comprising SNAC and a GLP-1 peptide (see e.g. documents D20, D24 and D30).

29. As also indicated in the decision under appeal, the general principle of formulating different components of an oral pharmaceutical composition into different granules was well known and established (see e.g. documents D17, D18, D20, D25 and D37).

30. Document D17 on page 330, last two paragraphs, discloses that:

> "*Acidic and alkaline ingredients are granulated separately. The two granules are then mixed together, just before adding the lubricant for tableting.*".

31. As pointed out by the appellant, this passage relates to the specific case of "incompatible" ingredients which are separated into different granules in a tablet. The skilled person would thus not have applied this teaching to solve the problem of providing an alternative formulation for two compatible ingredients (salt of NAC and GLP-1 peptide).

32. Document D18 on page 159 in paragraph 2 discloses: "*Another example of the relation of dose uniformity and number of particles in the dose is found with two components that are separately granulated before mixing. This procedure is sometimes adopted for reasons of stability during granulation.*"

33. Document D20 states in paragraph [66]:

> "*where particles, micro-beads, or granules of an active agent are prepared separately from particles, micro-beads, or granules of a delivery agent compound, the active agent particles, micro-beads, or granules will, generally, not comprise delivery agent compound, and the delivery agent particles, micro-beads, or granules will, generally, not comprise active agent, though each particle, micro-bead, or granule may comprise other ingredients, as disclosed herein*".

34. The appellant considers this passage of document D20 as less relevant because it only related to "*Definitions*" (see title of the respective section). The board does not agree, because the separate granulation of an active agent and a delivery compound is disclosed, whether as a definition or as an embodiment. In any case, the following paragraph [67] in the same section also lists "embodiments".

35. Document D20 furthermore discloses SNAC as a delivery agent (see claim 40) and GLP-1 as an active agent (see claim 44).

36. A further relevant teaching can be found in document D25, page 18, paragraph 54:

> "*the multiparticulate oral dosage form may comprise a blend of two or more populations of particles, granules, pellets, or mini-tablets having different agents to be delivered. For example, one population of particles may include the enhancer, and another population of particles may include the drug (e.g., romidepsin)*"

37. Document D29 refers in paragraph 16 to: "*wet granulating* [...] *SNAC or a mixture thereof (with or without one or more active agents* [...])" and document D31 mentions in paragraph [109]: "*separately preparing delivery agent granules and gallium salt granules*".

38. The argument by the appellant that the "enhancer" in some of the disclosures above was "broadly defined" is not considered relevant, because the skilled person was able to apply the two-granule concept to the enhancer at hand, i.e. SNAC as disclosed in document D2. Similarly, the argument that the cited documents related to other active ingredients (e.g. gallium salt in D31) cannot convince the board, because the skilled person was looking for an alternative formulation and had no reason not to consider the proposed solution as applicable to the combination of a GLP-1 peptide with SNAC, which is disclosed as a delivery agent for oral pharmaceutical compositions in document D31 (see e.g. paragraphs [0029] and [0087], claim 23). Documents D20 (see page 32, line 13), D24 (see paragraph [0049]) and

D30 (see paragraph [108]) furthermore mention a GLP-1 peptide as active ingredient in a "two-granule format".

39. It was also common general knowledge that the composition of granules could be adapted individually to the requirements of a particular ingredient in each type of granules, e.g. to influence the release profile. This concept is disclosed in document D25, page 19, lines 1 to 4:

> "*The multiparticulate oral dosage form may also comprise a blend of two or more populations of particles, granules, pellets, or mini-tablets having different in vitro and/or in vivo release characteristics.*"

40. As mentioned in the decision under appeal, this concept is also disclosed in the review article D37, page 3, left-hand column, second paragraph:

> "[...] *multiple-unit dosage forms comprise of* [sic] *number of discrete particles that are combined into one dosage unit. They may exist as pellets, granules* [...] *multiple-unit dosage forms offer several advantages over single-unit systems such as non-disintegrating tablets or capsules [4].* [...] *In the multiple-unit system, the total drug is divided into many units* [...] *Other advantages of this divided dose include ease of adjustment of the strength of a dosage unit, administration of incompatible drugs in a single dosage unit by separating them in different multiparticulates and combination of multiparticulates with different drug-release rates to obtain the desired overall release profile.*"

41. The skilled person was therefore aware of the possibility of formulating GLP-1 peptide into one

granule type, which was mixed with other granules containing no GLP-1 peptide, but for example enhancers. Equally, the skilled person was aware that a salt of an NAC could be formulated into one granule type which was mixed with other granules containing for example active agents. The skilled person furthermore knew about the possibility of achieving different release characteristics for different ingredients in separate types of granules, i.e. of releasing one compound faster or more slowly than the other. The skilled person aiming at an alternative pharmaceutical composition would thus have modified the tablet composition disclosed in document D2 by formulating semaglutide and SNAC into separate granules.

42. In conclusion, the skilled person would have arrived in an obvious manner at the subject-matter of claim 1, which is thus not inventive within the meaning of Article 56 EPC.

Auxiliary request 1
Claim interpretation

43. Claim 1 contains the feature "wherein the release of said salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid is faster than the release of said GLP-1 peptide as determined by dissolution testing using Assay (I) at pH 2.5, as described herein".

44. "Faster" release is not a term of art. The claim does not define what "faster" release means other than that it is determined by Assay (I) at pH 2.5. This wording is not open to an objection under Article 84 EPC because it was present in dependent claim 2 of the patent as granted (see decision G 3/14). It, however,

has to be interpreted in its broadest technically meaningful sense.

45. Assay (I) is described in paragraph [0100] of the patent. It involves a standard dissolution test "*according to United States Pharmacopeia 35*" at three different pH values, pH 1.0, pH 2.5 or pH 6.8. Sample aliquots are removed at appropriate intervals and analysed by RP-HPLC for the content of SNAC and GLP-1 peptide (e.g. semaglutide). The sample contents are calculated based on the relevant peak areas relative to the peak areas of a reference sample and the "*released amounts of SNAC and GLP-1 (e.g. semaglutide) were calculated as percentages of the nominal contents in the tablet*".

46. The term "faster" implies the determination of a rate of release, i.e. a released amount per time unit. Assay (I) in paragraph [0100], however, does not define how to calculate such rate of release. Establishing the rate of release requires at least knowledge of (i) the amount of the released compounds, (ii) the dimension of this amount (e.g. mass, molar, percentage) and (iii) the relevant time period.

47. The "released amounts" in Assay (I) are "calculated as percentages" (see also Tables 4 to 8 in the patent), i.e. as a fraction of the amount present in the composition as a whole. The functional limitation in the claim "the release of said salt of NAC is faster than the release of said GLP-1" can be interpreted in two ways:

1) as the release of a given relative amount of a salt of NAC in a shorter period of time, i.e. faster, compared with the release of the same relative amount of GLP-1 when starting from a given

time point. For example, when starting at time point 0, 19% of the total amount of SNAC in the tablet is released within 5 minutes while 20% of the total amount of semaglutide is released only within about 12 minutes (see Composition B in document D40 and Table 4 of the patent), or
2) as the release of a greater relative amount of a salt of NAC compared with the relative amount of GLP-1 released over the same period of time. For example, from 0 to 10 minutes 28% of the total amount of SNAC is released but only 17% of the total amount of semaglutide (see composition B in document D40 and Table 4 of the patent).

48. Time points at which samples are to be taken or a time period for which the rate of release is to be calculated are provided neither in the claim nor in paragraph [0100] of the patent. In paragraph [0018] the patent states that the release "*is determined within 30 minutes, such as within 25, 20, 15 minutes, or such as within 10 or 5 minutes*".

49. The appellant's argument that the skilled person would interpret "the release is faster" as implying a time interval in the beginning of the dissolution test (e.g. between 0 minutes and about 10 to 15 minutes) cannot be accepted because the claim contains no limitation in this regard and such interpretation would not be derivable from the description as a whole or from common general knowledge either.

50. The feature "wherein the release ... is faster" is thus interpreted in its broadest technically meaningful sense: either a higher percentage of a salt of NAC than of GLP-1 peptide is released over the same time period or a given percentage of a salt of NAC is released in a

shorter time period than the same percentage of GLP-1 peptide.

Inventive step (Article 56 EPC)

51. It was undisputed that document D2 represents a suitable starting point for assessing inventive step. The first difference of the claimed subject-matter from the disclosure of document D2 is the presence of a salt of NAC and GLP-1 in different granules (see points 2. and 4. above).

52. The parties differed on the question of whether the functional feature "wherein the release [...] is faster" represented a further difference.

53. As established above, Assay (I) can be carried out at various time points. To calculate a release rate at least two time points are necessary, one of which could be at 0 minutes, i.e. no release. In the initial 20 minutes, compositions B and F show a "faster" release of SNAC than of semaglutide, while composition D, which can arguably be taken as representative of composition B in document D2 (see point 12. above), shows a slower release of SNAC than of semaglutide (see document D40).

54. The respondents argue that composition E, which is a further single-granule-type composition tested in the patent, was also representative of the prior art. Composition E fell under embodiment 44 on page 23 of document D2, which reads as follows:

> "*44. A composition according to any one of the preceding embodiments, wherein said composition comprises at least 60% (w/w) delivery agent, less than 10% (w/w) binder, 5-40% (w/w) filler, and less than 10% (w/w) lubricant and/or glidant.*"

Composition E showed a faster release of SNAC compared with semaglutide, at least in the first 10 minutes (see Table 8 and document D40).

55. The board considers composition E not adequately representative of the cited prior art. The features of embodiment 44 in document D2 are defined by open-ended ranges of excipient classes and combinations of features of "*any one of the preceding embodiments*", so no specific composition corresponding to composition E in the patent is in fact disclosed. Moreover, composition E of the patent does not contain MCC in the extragranular part, which is common to all compositions made and tested in document D2 (see Table 1).

56. Since the release profiles for the exact compositions disclosed in document D2 are not known and in view of the comparative data for compositions D, B and F in the patent (see point 53. above), the board starts from the assumption, in favour of the appellant, that the faster release of a salt of NAC represents a further difference from the disclosure of document D2.

57. This difference, however, is not linked to a technical effect, as will be explained in the following. For a pharmaceutical composition the relative *in vitro* release rate of individual compounds (e.g. "faster") is only meaningful if it is linked to a physiologically relevant parameter, in the present case bioavailability. Achieving a "faster release" of SNAC than semaglutide in an *in vitro* assay without any effect on bioavailability of the active ingredient, i.e. semaglutide, *in vivo* would be a mere arbitrary measure.

58. It therefore has to be asked whether the "faster release" of SNAC as required by the claim translates into higher bioavailability of semaglutide over the whole breadth of the claim as alleged by the appellant.

59. The time period in which a "faster release" occurs is not defined in the claim and can potentially be very short or very long. Neither for very small time periods (e.g. a few seconds) nor for very long time periods (e.g. days) can a positive effect on bioavailability be credibly expected.

60. Furthermore, the relative parameter "faster" includes very small differences in the release rate, such as those seen for composition E at 5 and 10 minutes (see Table 8 and document D40), which are unlikely to have any substantial effect on bioavailability, and there is no data on file in this regard.

61. In addition, the respondents have argued that very large differences in release rate could lead to a situation where the GLP-1 peptide is no longer co-released with a salt of NAC, so that the two cannot interact, leading to an effective decrease in bioavailability (see decision under appeal, sheet 49, first paragraph; see also document D11, page 15, right-hand column, last paragraph: "*SNAC enhances absorption by forming a noncovalent complex with the active compound that enables transcellular absorption, without altering tight junctions*"). It is therefore not credible that very small or very large differences in the release rates would achieve improved bioavailability of GLP-1 peptide.

62. This disconnect between the "faster release" *in vitro* and *in vivo* bioavailability (see points 59. to 61.

above) is aggravated by the fact that the relative amounts of a salt of NAC and of GLP-1 peptide are not defined in the claim. In all the examples in the patent, however, the mass ratio between SNAC and semaglutide is 30:1, which because of the different molecular weights of the compounds translates into a molar ratio of about 300:1. Substantially changing this molar ratio would likely abolish any potentially existing effects of different release rates.

63. In conclusion, the board considers it not credible that an effect on bioavailability is achieved under all conditions and thus across the whole scope of the claim.

64. The objective technical problem can thus be formulated identically to that for the main request as being to provide an alternative pharmaceutical composition comprising a salt of NAC and GLP-1 peptide.

Obviousness

65. In view of the lack of a technical effect (see points 59. to 63. above) "the release of a salt of [NAC] faster than the release of said GLP-1 peptide" is considered arbitrary and cannot contribute to an inventive step. The same reasoning as for claim 1 of the main request therefore applies.

Auxiliary request 5
Admittance (Article 12(2) and (3) RPBA)

66. The request forms part of the appeal, as it has been dealt with in the decision under appeal (Article 12(2) RPBA). In accordance with Article 12(3) RPBA, the request was also substantiated

in appeal (see statement of grounds of appeal, points 5.18 to 5.21). The board therefore has no discretion to reverse the decision of the opposition division to admit the request unless the opposition division had exercised its discretion according to the wrong principles, or without taking into account the right principles, or in an unreasonable way, and had thus exceeded the proper limits of its discretion (T 640/91, OJ 1994, 918; G 7/93, OJ 1994, 775). The criterion of "convergence" invoked by respondent III in appeal appears not to have been relevant to the admission of what was then auxiliary request 5A (see point 55.1 of the decision under appeal and points 105 to 113 of the minutes of the oral proceedings before the opposition division). Rather, the opposition division found that the request had been filed in reaction to at least one ground of opposition (lack of inventive step), and that the amendments were of a simple nature, clear and intended to overcome said ground of opposition. They addressed the opposition division's position in relation to auxiliary request 5 which was expressed for the first time during the oral proceedings. The board finds no error in this discretionary decision by the opposition division.

Inventive step (Article 56 EPC)

67. Claim 1 contains the following limitations for the amount and type of components in the composition:
overall at least 60 % (w/w) the salt of NAC
first type of granules comprises
- a salt of NAC
- no GLP-1 peptide
- at least 75 % (w/w) of a salt of NAC
- less than 10 % (w/w) lubricant
- optionally less than 20 % (w/w) filler

second type of granules comprises
- a GLP-1 peptide, a binder and a filler
- no salt of NAC
- at least 15 % (w/w) filler
- less than 40 % (w/w) binder

extragranular part consists of a lubricant.

68. The requirement that the composition as a whole comprises at least 60 % (w/w) salt of NAC and that the first type of granules comprise at least 75 % (w/w) salt of NAC does not further distinguish the composition from the prior art because composition B of document D2 contains 300 mg SNAC in a 400 mg tablet, i.e. 75% of the tablet composition as a whole, and about 96% of the granule.

69. The requirement that the first type of granules comprise "less than 10 % (w/w) lubricant" indisputably includes concentrations close to 0% lubricant. Whether "less than" also includes no lubricant is irrelevant to the decision because very small amounts of lubricant are not associated with any technical effect. The same applies to the "optional" presence of filler in the first type of granules.

70. The requirement that the second type of granules comprise "less than 40 % (w/w) binder" equally includes concentrations close to 0 % binder. This feature thus has no technical effect either. The only potentially relevant excipient amount is therefore "at least 15 % filler" for the second type of granules. No evidence has been provided, however, that this lower limit for the amount of filler might be linked to any technical effect.

71. The requirement that the extragranular part consist of lubricant, i.e. contain no other components, represents a further difference compared with composition B of document D2, which contains in addition the filler Avicel PH 102. The absence of filler in the extragranular part, however, has not been argued by the appellant to be linked to any particular technical effect. Moreover, document D2 itself teaches that: "*The extragranular part may comprise a filler, a lubricant and/or a glidant.* [...] *In some embodiments the extragranular part comprises magnesium stearate.*" (page 13, lines 30 to 31). It was thus obvious to the skilled person that the extragranular part could also only consist of Mg stearate, which is a lubricant.

72. The claim therefore contains no further distinguishing features which might contribute an additional effect. The objective technical problem is therefore the same as for claim 1 of the main request and auxiliary request 1, namely to provide an alternative pharmaceutical composition comprising a salt of NAC and GLP-1 peptide.

Obviousness

73. The skilled person would have routinely used and tested different excipient classes, e.g. filler, binder and lubricant, in the granules. The skilled person would also have routinely adapted the amounts of these excipients to obtain a composition suitable for pharmaceutical use and therefore arrived at the claimed subject-matter.

74. The subject-matter of claim 1 lacks an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

A. Vottner M. Pregetter

Decision electronically authenticated