

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2022/085558

International filing date (day/month/year)
13.12.2022

Priority date (day/month/year)
13.12.2021

International Patent Classification (IPC) or both national classification and IPC
INV. A61K38/22 A61K38/26 A61P3/00 A61P9/00 A61P25/28 A61K47/02 A61K47/10 A61K9/08

Applicant
NOVO NORDISK A/S

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-15</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-15</u>
Industrial applicability (IA)	Yes: Claims	<u>1-15</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents and the passages identified in the International Search Report; the numbering will be adhered to in the rest of the procedure:

- D1 WO 2021/152184 A1 (ADOCIA [FR]) 5 August 2021 (2021-08-05)
- D2 KAKOURI AGNI ET AL: "New Incretin Combination Treatments under Investigation in Obesity and Metabolism: A Systematic Review", PHARMACEUTICALS, vol. 14, no. 9, 28 August 2021 (2021-08-28), page 869, XP055917072, DOI: 10.3390/ph14090869
- D3 BECERRIL SARA ET AL: "Cagrilintide plus semaglutide for obesity management", THE LANCET, ELSEVIER, AMSTERDAM, NL, vol. 397, no. 10286, 22 April 2021 (2021-04-22), pages 1687-1689, XP086569913, ISSN: 0140-6736, DOI: 10.1016/S0140-6736(21)00944-2 [retrieved on 2021-04-22]
- D4 WO 2007/022518 A2 (AMYLIN PHARMACEUTICALS INC [US]; BARON ALAIN D [US] ET AL.) 22 February 2007 (2007-02-22)
- D5 WO 2008/073448 A2 (AMYLIN PHARMACEUTICALS INC [US]; JENNINGS ROBERT N JR [US] ET AL.) 19 June 2008 (2008-06-19)

D1 refers to a liquid composition i.e. solution comprising an amylin receptor agonist and a GLP-1 receptor agonist (GLP-1 RA) i.e. exenadite for use in treating obesity or diabetes; wherein the pH of the solution is ranging from 6.8 to 7.4; comprising a buffer, tonicity agent sodium chloride and a surfactant i.e. polysorbate;

D2 refers to amylin receptor agonist **cagrilintide** which is a long-acting acylated amylin analogue that is combined with GLP-1 receptor **semaglutide** and leading to greater weight loss compared to semaglutide monotherapy; A total of 96 individuals were enrolled in the study and the results showed a 15.7%

bodyweight reduction from base-line with 1.2 mg cagrilintide and 17.1% reduction with 2.4 mg cagrilintide compared to placebo; both in combination with semaglutide 2.4 mg;

D3 refers to once-weekly subcutaneous concomitant administration of one of six multiple-ascending doses of **cagrilintide** (range 0.16-4.5 mg; n=11-12 per group) or placebo (n=24), both with **semaglutide**, at the fixed dose of 2.4 mg; thus, the cagrilintide plus semaglutide combination has the potential to act additively to improve weight control; acceptable safety and tolerability of the cagrilintide plus semaglutide combination while providing substantial weight loss in this study group.

D4 refers to a liquid composition comprising a GLP-1 receptor agonist such as exenadite or amylin receptor agonist such as amylinomimetics in combination with cyclodextrins including a hydroxypropyl such as 2.5% to 10% hydroxypropyl- beta-cyclodextrin as **solubility enhancer**; water for injection, a tonicity agent sodium chloride, a buffer, a surfactant i.e. polysorbate 80; for use in treating diabetes, nonalcoholic steatohepatitis (NASH); the combination of incretin being GLP-1 receptor agonist and amylinornimetic is suggested not exemplified;

D5 refers to a solution comprising a peptide such as amylin or a GLP-1 receptor agonist exendin and a cyclic oligosaccharide being a cyclodextrin such as hydroxypropyl-[beta]- cyclodextrin.

- 2 The present application refers to a liquid pharmaceutical formulation comprising an amylin receptor agonist such as cagrilintide and a GLP-1 receptor agonist such as semaglutide being exemplified and a cyclodextrin comprising hydroxypropyl substitutions. Said co-formulation may be used for the medical treatment of subjects with obesity, diabetes, cardiovascular diseases, non-alcoholic steatohepatitis (NASH) and cognitive impairment, such as that caused by Alzheimer's disease.

- 3 Novelty - Art. 33 (2) PCT

The subject-matter of present claims 1-15 is novel in view of the cited documents D1 - D5 as none of said documents describes the combination of all three compounds i.e. amylin receptor agonist and GLP-1 receptor agonist and cyclodextrin comprising hydroxypropyl substitutions in one liquid pharmaceutical formulation.

In D4 all three compounds are mentioned, however, the combination of GLP-1 receptor agonist and amylin receptor agonist is suggested but not exemplified.

4 Inventive step - Art. 33 (3) PCT

The closest prior art is represented by D1, D2, D3 or D4 all referring to a pharmaceutical combination comprising of amylin receptor agonist and a GLP-1 receptor agonist (GLP-1 RA) for use in treating obesity and diabetes.

The essential feature distinguishing the present claims from the closest prior art is

a pharmaceutical composition comprising the **combination of all three** compounds a) i.e. amylin receptor agonist and b) GLP-1 receptor agonist **and** c) cyclodextrin comprising hydroxypropyl substitutions in one liquid pharmaceutical formulation.

In Example 1 of the present application the effect of hydroxypropyl-beta-cyclodextrin (HP-B-CD) on the chemical stability of cagrilintide is shown.

In Example 2 it is shown that when semaglutide was stored at pH 6 and in the absence of HP-B-CD (semaglutide formulation 1), fibrillation occurred after about 2.35 hours; that is, semaglutide was not physically stable. When semaglutide was stored at pH 6 and in the presence of HP-B-CD, fibrillation was not observed during the duration of the experiment; that is, semaglutide was physically stable.

In Example 4 the effect of molar substitution of HP-B-CD on cagrilintide and semaglutide co-formulation physical stability is shown such as the effect of different molar substitution of HP-B-CD on the cagrilintide and semaglutide co-formulation in form of subvisible particle count and ThT fluorescence intensities.

The problem of the present application is defined as the provision of a further pharmaceutical composition comprising a combination of i.e. amylin receptor agonist and GLP-1 receptor agonist for use in treating obesity, diabetes, cardiovascular disease or non alcoholic steatohepatitis and cognitive impairment.

The solution is considered to be obviously derivable from D1, D2, D3 or D4 and the skilled person's knowledge or in view of D1 - D4 in combination with D5 already suggesting hydroxypropyl-[beta]-cyclodextrin and amylin or a GLP-1 receptor agonist extendin a solubility agent.

Therefore the subject-matter of the present claims are not allowable under Art. 33 (3) PCT.

Re Item VIII

Certain observations on the international application

5 Arts. 5 and 6 PCT

- 5.1 Claims 1, 14 and 15 do not comply with the requirements of Article 5 and 6 PCT, for the following reasons. The claims are directed to a therapeutic use of certain compounds, i.e. amylin receptor agonist and GLP-1 receptor agonist, which are defined only in terms of their functional activity.

All three following conditions need to be fulfilled to allow a functional definition of a compound:

- 1) the compounds showing the desired functionality are part of the common general knowledge and the functionality is accepted in the prior art to have a clear technical meaning
- 2) the functionality can be verified using tests or procedures adequately specified in the description or known to the skilled person and which do not require undue experimentation, and
- 3) the invention is described not only in terms of its structure, but also in terms of its function, unambiguously showing that the functional activity is essential or the solution of the technical problem underlying the invention, regardless of the structure of the compounds.

In the present case, conditions 1-3 are have not been fulfilled as an unlimited number of amylin receptor agonists and GLP-1 receptor agonists exist and merely one agonist each has been exemplified such as cagrilinitide (amylin receptor agonists) and semaglutide (GLP-1 receptor agonist). This functional terms do not give a specific technical guidance for the ascertainment of the scope of the claim as to which compounds are suitable having the desired function without imposing an unreasonable burden, and thus can be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable.

- 5.2 Although claims 1, 12 and 13 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.
- 5.3 The wording "overweight" or "cognitive impairment" of claim 15 does not clearly represent a true pathological condition.

Therefore claim 15 does not represent a true second medical use type claim for all the claimed features.