

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

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/US2016/037818	International filing date (day/month/year) 16.06.2016	Priority date (day/month/year) 22.06.2015
International Patent Classification (IPC) or both national classification and IPC INV. A61K38/00 A61K38/26 C07K14/605 C07K14/00 A61P3/00 A61P1/00		
Applicant ELI LILLY AND COMPANY		

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:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Zellner, Eveline Telephone No. +49 89 2399-0	
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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:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
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>1-44</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-44</u>
Industrial applicability (IA)	Yes: Claims	<u>1-44</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

- 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 2011/094337 A1 (UNIV INDIANA RES & TECH CORP [US]; DIMARCHI RICHARD D [US]; MAT TAO [U] 4 August 2011 (2011-08-04)
- D2 CA 2 852 177 A1 (UNIV INDIANA RES & TECH CORP [US]) 23 December 2009 (2009-12-23)
- D3 WO 2013/074910 A1 (UNIV INDIANA RES & TECH CORP [US]) 23 May 2013 (2013-05-23)
- D4 WO 2013/004983 A1 (IMP INNOVATIONS LTD [GB]; BLOOM STEPHEN ROBERT [GB]) 10 January 2013 (2013-01-10)
- D5 WO 2014/152460 A2 (UNIV INDIANA RES & TECH CORP [US]) 25 September 2014 (2014-09-25)

- 2 Claims 29-33 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1 (iv)/67.1 (iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

3 **Re Item V**

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

Novelty - Art. 33 (2) PCT

D1 refers to Gip agonist peptides being at least 94 % similar to SEQ ID NO:2 of the present application comprising Aib at position 2, Glu at position 16, Lys at position 20, further comprising a linker such as polyethylene glycol, with fatty acid C14 to C28, 20K-PEG-Mal, a linker at position 20 K being 6-amino hexanoic acid, 5-aminovaleric acid, 7-aminoheptanoic acid, and 8-amino-octanoic acid for use in the treatment of diabetes, obesity, fatty liver.

D2 refers to glucagon or oxyntomodulin peptides or its salt being more than 94% identical, having Glu at position 16 (E16), Lys at position 20 (K20), Aib at position 2, a C16, C18, C24, fatty acid, a linker i.e. a PEG linker, at position 20, or the linker is a dimer Cys, a dimer Pro, the linker is an amino acid backbone that is 3 to 10 atoms in length (e.g., 6-amino hexanoic acid, 5-aminovaleric acid, 7-aminoheptanoic acid, and 8-aminooctanoic acid). Said peptides are for use in the treatment of diabetes type 2 or obesity.

D3 refers to glucagon superfamily peptides being 94% identical with SEQ ID NO:2 of the present application having T29G, S16E, N20K, a C14 to C24 fatty acid linked thereto, via a polyethylene glycol, the spacer amino acid can be an acidic residue, e.g., Asp and Glu the spacer amino acid can be a hydrophobic amino acid, e.g., Gly, Ala, Val, Leu, Ile, Trp, Met, Phe, Tyr, 6-amino hexanoic acid, 5-aminovaleric acid. In some embodiments, the acyl group is a fatty acid or bile acid, or salt thereof, e.g. a C4 to C30 fatty acid, a C8 to C24 fatty acid, cholic acid, a C4 to C30 alkyl, a C8 to C24 alkyl, or an alkyl comprising a steroid moiety of a bile acid. The spacer is any moiety with suitable reactive groups for attaching acyl or alkyl groups. The spacer comprises an amino acid, a dipeptide, a tripeptide, a hydrophilic bifunctional, or a hydrophobic bifunctional spacer. In some embodiments, the spacer is selected from the group consisting of: Trp, Glu, Asp, Cys and a spacer comprising $\text{NH}_2(\text{CH}_2\text{CH}_2)_n(\text{CH}_2)_m\text{COOH}$, wherein m is any integer from 1 to 6 and n is any integer from 2 to 12. Such acylated or alkylated glucagon peptides may also further comprise a hydrophilic moiety, optionally a polyethylene glycol for use in the treatment of obesity or diabetes.

D4 refers to glucagon like peptides being 94% identical with SEQ ID NO:2 of the present application linked to fatty acids for use in the treatment of diabetes type 2; PEGylated compounds provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity. The peptides are nearly identical with the peptides of the present application with the exception of amino acid at position 18 and at position 28.

D5 refers to glucagon like peptides comprising a C14, or C24 fatty acid, a spacer comprising one or more amino acids selected from the group consisting of Cys, Lys, Orn, homo-Cys, and Ac-Phe., the spacer amino acid can be a hydrophobic amino acid, e.g., Gly, Ala, Val, Leu, Trp, Met, Phe, Tyr,

6-amino hexanoic acid, 5-aminovaleric acid, 7-aminoheptanoic acid, 8-aminooctanoic acid. Said peptides are for use in the treatment of diabetes or obesity.

The peptides of the present application are distinguished from the D1 to D5 by at least two amino acids.

Therefore, the present set of claims are novel in view of D1 to D5.

4 Inventive step - Art. 33 (3) PCT

The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of claims 1 - 44 does not involve an inventive step.

4.1 D1 to D5 may be regarded as being the prior art closest to the subject-matter of claim 1 - 44.

As pointed out under novelty said documents all refer to glucagon like peptides chemically modified by conjugating linkers and fatty acids.

The essential difference of the conjugated peptides of the present application and said documents are a few amino acids.

No particular effect has been demonstrated in comparison with the peptide conjugates of the present application.

The problem is the provision of further peptides and their conjugates for use the treatment of diseases such as obesity or diabetes type 2.

The solution are peptides as disclosed in the present set of claims (especially 1 and 39).

Starting from D1 to D5 said peptides and its conjugates are obvious alternatives for the skilled person in view of his common general knowledge as he would have no difficulty in changing the amino acids, the linkers or the attached fatty acids.

Therefore, the subject-matter of Claims 1-44 does not involve an inventive step (Art. 33 (3) PCT).

5 Re Item VIII

Certain observations on the international application

The application does not meet the requirements of Article 6 PCT, because claim 5-22 are not clear.

The linker is defined by an unlimited number of alternatives is thus open for interpretation.