

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

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/US2020/043988

International filing date (day/month/year)
29.07.2020

Priority date (day/month/year)
01.08.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61K38/16 A61P3/10

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



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>1-30</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-30</u>
Industrial applicability (IA)	Yes: Claims	<u>1-30</u>
	No: Claims	

2. Citations and explanations

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 2019/125929 A1 (LILLY CO ELI [US]) 27 June 2019 (2019-06-27)
 - D2 US 2018/155407 A1 (BOSSART MARTIN [DE] ET AL) 7 June 2018 (2018-06-07)
 - D3 WO 2016/066744 A2 (ZEALAND PHARMA AS [DK]) 6 May 2016 (2016-05-06)
 - D4 WO 2016/111971 A1 (LILLY CO ELI [US]) 14 July 2016 (2016-07-14) cited in the application
 - D5 LORENZ MARTIN ET AL: "Recent progress and future options in the development of GLP-1 receptor agonists for the treatment of diabetes", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 23, no. 14, 16 May 2013 (2013-05-16), pages 4011-4018, XP028573319, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2013.05.022
- 2 Claims 24 -27 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 Novelty - Art. 33 (2) PCT

D1 refers to glucose- dependent insulinotropic polypeptide (GIP), glucagon-like peptide- 1 (GLP-1) and glucagon receptors agonist peptides; At position X17 Lys is chemically modified through conjugation to an e-amino group of a Lys side chain with (2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)a-(y Glu)b-CO-(CH₂)c-COOH; peptides are for use in treating obesity or diabetes mellitus type 2. The

peptides are defined in a formula such as
YX2X3GTX6TSDYSIX13LDKX17AQX20AFIEYLLEGGPSSGAPPPS, here X2 is
Aib, X3 is Q or H, X6 is aMeF or aMeF(2F), X13 is L or aMeL, X20 is Aib, Q or
H and the C-terminal amino acid is optionally amidated, or a pharmaceutically
acceptable salt thereof.

The peptides of D1 correspond to formula 1 of the present application and claim
1. The distinguishing feature is that X3 is E followed by GT in the present
application whereas X3 is Q or H in D1.

Therefore the subject-matter of present claims is novel in view of D1.

D2 refers to GLP1, Glucagon like peptide, GIP receptor agonist peptides for use
in treating obesity or type 2 diabetes wherein Lys residues having (2-(2-
aminoethoxy)ethoxy) acetyl groups.

At position X14 is M or Lys, Orn, Dab, or Dap in D2 whereas in the present
application X14 is Leu.

Therefore the the subject-matter of present claims are novel in view of D2.

D3 refers to GIP receptor agonist peptides for use in treating diabetes type 2 or
obesity; Formula 1 of D3 is identical with formula 1 of the present application.

In difference to the present application X17 or X26 are not modified as being
K(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)2 -(y-Glu)-CO-(CH₂)_q-C(=O)H;

Therefore the subject-matter of claims 1-30 is novel in view of D3.

D4 refers to GIP and GLP-1 agonist peptides for use in treating diabetes type 2
or obesity. In D4 there is a T at X7 instead of I (Ile) at position 7 (ISDY);
position 20 K has a side-chain modified with ([2-(2-Amino-ethoxy)-ethoxy]-
acetyl)2-(yGlu)-CO-(CH₂)_b-C(=O)H: C17 or X26 do not have the ethoxy side
chain.

Therefore the subject-matter of claims 1-30 is novel in view of D4.

D5 refers to GLP-1 receptor agonists comprising aminoethoxy-ethoxy-acetyl
groups. Said peptides have similar but not identical amino acid sequences for
use in treating obesity or diabetes type 2.

Therefore the subject-matter of claims 1-30 is novel in view of D5.

4 Inventive step - Art. 33 (3) PCT

The closest prior art is represented by D1 teaching glucose- dependent insulinotropic polypeptide (GIP), glucagon-like peptide- 1 (GLP-1) and glucagon receptors agonist peptides for use in treating obesity and diabetes mellitus type 2.

The distinguishing feature is one amino acid at position 3 i.e. X3 is E followed by GT in the present application whereas X3 is Q or H in D1.

The effect shown in the present application is that the peptides as disclosed in the examples (SEQ ID NO: 5, 6, 7, 8, 9 , 10 and 11) are consistent with an extended pharmacokinetic profile (Table 4) .

The data provided by Table 5 and 6 demonstrate a dose dependent increase in insulin secretion.

The data show that the frequency of positive CD4+ T cell response ($CDI > 2.5$) was low for the tested Example compounds, and the magnitude of the response in the one positive donor from the Example 2 group was low ($CDI < 3$). Thus, based on this assay, these compounds have a low risk of immunogenicity.

The problem is the provision of further stable agonist peptides for use in treating obesity or diabetes type 2.

The solution is considered to be obvious in view of D1 alone or in view of D1 and the combination of D1 with any of D2- D5.

Therefore the subject-matter of claims 1-30 is not allowable under Art. 33 (3) PCT.