

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/IB2019/052835

International filing date (day/month/year)
05.04.2019

Priority date (day/month/year)
05.04.2018

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/605 A61K38/26

Applicant
SUN PHARMACEUTICAL INDUSTRIES LIMITED

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

Gómez Ortiz, Mariola

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>1-10</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-10</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-10</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Re Item V

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

Reference is made to the following documents:

- D1 WO 2006/097537 A2 (NOVO NORDISK AS [DK]; LAU JESPER [DK] ET AL.) 21 September 2006 (2006-09-21) cited in the application
- D2 WO 2006/097538 A1 (NOVO NORDISK AS [DK]; LAU JESPER [DK] ET AL.) 21 September 2006 (2006-09-21)
- D3 WO 2018/178796 A1 (SUN PHARMACEUTICAL INDUSTRIES LTD [IN]) 4 October 2018 (2018-10-04)

The present claims are directed to GLP-1[7-34] analogues comprising a Ser or Ala or Aib residue at the second position (8), wherein X34 is absent and there is a Leucine or Isoleucine C-terminal residue. The Lysine at position 21 (26) is acylated with the groups U-W-Y-Z as in claim 1.

Prior art:

None of the cited prior art documents discloses the peptide of claim 1 because there appears to be no GLP-1 analogue with the C-terminal as claimed.

There are several documents which published GLP-1 analogues acylated with similar groups as the claimed ones at Lysine 21(26):

D1 (Pages 19-22, claims 9, 28, Examples) is considered to be the closest prior art: discloses acylated semaglutide with groups very similar to the ones of the present claim 1.

D2 discloses similar acyl groups attached to a Lys at position 34 (37 or 38) (C-terminal). Peptide with Leu or Ile at the C-terminal not published, therein.

Novelty (Art. 33(2) PCT) and inventive step (Art. 33(3) PCT):

Present claim 1 differs from the GLP-1 of D1 in the C-terminal amino acid which is a Leucine or an Isoleucine:

Semaglutide with Aib at X2: HA**ib**EGTFTSDV SSYLEGQAAK EFIAWLVRGR G

Present claims: HA**ib**EGTFTSDV SSYLEGQAAK EFIAWLVRGR GL

The acylation is in the same position and very similar groups are attached.

The technical effect according to the comparative examples is:

better in terms of glucose reduction, food intake and body weight reduction and in duration of action .

The problem to be solved is to provide a better GLP-1 analogue than semaglutide.

The solution are the acylated peptides of claim 1.

This solution is not obvious as non being suggested by the prior art : the addition of an Leu or Ile is not predictable from the prior art and the effect is as well not obvious for the skilled person.

Re Item VI

Certain documents cited

D3 (compound 6P-E on page 18) discloses a polypeptide falling under the scope of claims 1 and 9 of the present application. However, the peptide is not acylated at the Lysine 26 position. Acylation is in general mentioned but not specifically and not with this peptide. In addition, this document does not is related to method for making KEX1 protease-sensitive polypeptides in yeast and not with the development of more effective GLP-1 analogues. Therefore, it is not relevant.