

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
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International application No. PCT/US2019/024756	International filing date (day/month/year) 29.03.2019	Priority date (day/month/year) 06.04.2018
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International Patent Classification (IPC) or both national classification and IPC INV. C07K14/495
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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 Keller, Yves 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>1-22</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-22</u>
Industrial applicability (IA)	Yes: Claims	<u>1-22</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

Reference is made to the following documents:

- D1 WO 2017/109706 A1 (NOVARTIS AG [CH]) 29 June 2017 (2017-06-29)
- D2 US 2016/120999 A1 (SHEN WENYAN [US] ET AL) 5 May 2016
(2016-05-05)
- D3 YUMEI XIONG ET AL: "Long-acting MIC-1/GDF15 molecules to treat
obesity: Evidence from mice to monkeys",
SCIENCE TRANSLATIONAL MEDICINE,
vol. 9, no. 412, 18 October 2017 (2017-10-18), page eaan8732,
XP55593022,
US
ISSN: 1946-6234, DOI: 10.1126/scitranslmed.aan8732

D1 disclose compounds comprising an Fc domain fused to GDF15. The Fc domain is fused via a linker to the other moiety (GDF15).

Said compound can be used in therapy and in particular for the treatment of NASH, NAFLD, and other liver diseases (abstract; paragraph [0012]; paragraph [0015]; paragraph [0018] - paragraph [0021]; paragraph [0065] - paragraph [0073]; paragraph [0151] - paragraph [0230]; claims 1-24).

D2 discloses compounds comprising an Fc domain fused to GDF15. The Fc domain is fused via a linker to the other moiety (GDF15). Said compounds can be used in the treatment of body weight disorders, or glucose disorders. D2 discloses also a compound (SEQ ID No 63) having 90% identity with SEQ. ID No 2 of the present application (abstract; claims 1-84; sequence 63)

D3 discloses that compounds comprising an Fc domain fused to GDF15 have an extended half life (the whole document).

D2 can be considered as being the closest prior art-

The main difference between D1 and the present application is the particular linker linking an Fc domain fused to GDF15 in a compounds.

The technical problem to be solved can be considered as the provision of a further compounds comprising an Fc domain fused to GDF15 via a linker.

Starting from D2 the skilled artisan would have tried to obtain further compounds comprising an Fc domain fused to GDF15.

Being also aware of D3 which teaches that the presence of a flexible linker in such compounds has several benefits (discussion, second paragraph, 3 last sentences).

Therefore using his general knowledge in combination with D2 the skilled artisan would have arrived to the claimed compound comprising SEQ ID No. 2.

Moreover the particular claimed compound does not show an unexpected/surprising effect for the skilled artisan on which inventive step could be based.

Hence, claims 1-4 do not meet the requirements of Art. 33(3) PCT.

Furthermore the use of such compounds comprising an Fc domain fused to GDF15 for the treatment of NASH, diabetes, obesity, dyslipidemia, is also straight forward for the skilled artisan as it was known in the art that said compounds can be used to treat said conditions. Therefore, the skilled artisan would have arrived to the claimed subject matter without inventive skills.

Hence, claims 1-22 do not meet the requirements of Art. 33(3) PCT.