PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

RECEIVED
SEP 11 2023
LILLY LEGAL

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2023/021637	10.05.2023	11.05.2022

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/14 A61K9/48 A61K31/437 A61P3/04 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 43*bis*.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 notifed the International Bureau under Rule 66.1*bis*(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:	Date of completion of this opinion	Authorized Officer
European Patent Office Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	see form PCT/ISA/210	Madalinska, K Telephone No. -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 43*bis*.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 13*ter*.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 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-29
	No:	Claims	
Inventive step (IS)	Yes:	Claims	4, 6, 7, 14-29
	No:	Claims	1-3, 5, 8-13
Industrial applicability (IA)	Yes:	Claims	1-29
	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:

D1 US 2019/225604 A1 (YOSHINO HITOSHI [JP] ET AL) 25 July 2019 (2019-07-25)

D2 JP 2019 099571 A (CHUGAI PHARMACEUTICAL CO LTD) 24 June 2019 (2019-06-24)

D3 KAWAI TAKAHIRO ET AL: "Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 117, no. 47, 24 November 2020 (2020-11-24), pages 29959-29967, XP093070947, ISSN: 0027-8424, DOI: 10.1073/pnas.2014879117 Retrieved from the Internet: URL:http://dx.doi.org/10.1073/pnas.2014879117

D4 WO 2008/030524 A2 (MERCK & CO INC [US]; BRESLIN DAVID [US] ET AL.) 13 March 2008 (2008-03-13)

D5 WO 02/064132 A2 (UPJOHN CO [US]; GAO PING [US]; MOROZOWICH WALTER [US]) 22 August 2002 (2002-08-22)

D6 WO 02/056878 A2 (PHARMACIA CORP [US]; GAO PING [US] ET AL.) 25 July 2002 (2002-07-25)

2 The relevant passages are those indicated in the search report, unless otherwise specified.

3 Regarding the novelty of claim 13 it is noted that the alleged "use in weight management" covers both a cosmetic and a therapeutic application of a claimed composition and hence in its present wording claim 13 only claims protection for a product that is suitable for the claimed use.

4 The expression "optionally" is to be regarded as entirely optional. This optional feature sets out in claims 16-17 has therefore no limiting effect on the scope of the invention.

5 The subject-matter of claims 1-29 is considered as meeting the requirements of Article 33(2) PCT for novelty.

D1 and D2 disclose (see text example 3) an oral liquid formulation comprising a compound 67, 3-[(1 S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one and a vehicle, said vehicle comprising DMSO (10 vol%): Cremophor EL (10 vol%): PEG 400 (15 vol%): 100 mM Glycine-NaOH buffer pH 10 (65 vol%), wherein glycine-NaOH buffer is considered as as a pH modifier. The liquid formulation of D1 is able to suppress a food intake and thus being used in the treatment of diabetes and weight complication. The liquid formulation of D1 and D2 is administered orally, but is not filled into capsules.

D1-D2 (see test example 2) and D3 (see page 29966, col. 2) disclose an oral liquid formulation comprising a compound 67 (D1, D2) or LY3502970 (D3), that is 3-[(1 S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one and 10% polyethylene glycol 400 / 10% propylene glycol / 80% glycine buffer (100 mM glycine, 64 mM NaOH, pH 10) buffer. Said liquid formulation of D1-D3 is however not filled into capsule.

Hence, it is concluded that none of the document in the priro art discloses an oral capsule composition comprising 3-[(1 S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one and a pH modifier.

Furthermore, also none of the documents in the prior art discloses a sprayed-dried dispersion comprising 3-[(1 S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one and a pH modifier.

The subject-matter of claims 1-29 meets thus the requirements of Article 33(2) PCT.

6 The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of claims 1-3, 5 and 8-13 does not involve an inventive step.

6.1 D1 is regarded as being the prior art closest to the subject-matter of claims 1 and 12-13 and discloses as mentioned above a liquid oral formulation comprising a compound 67 and a vehicle, said vehicle comprising DMSO (10 vol%): Cremophor EL (10 vol%): PEG 400 (15 vol%): 100 mM Glycine-NaOH buffer pH 10 (65 vol%).

The subject-matter of claims 1 and 12-13 therefore differs from this known in D1 that a liquid formulation is filled into an oral capsule.

There is no comparative data provided showing the surprising effect coming from a distinguishing feature that is coming form incorporating of a liquid formulation into a capsule, if compared with a formulation of D1.

The problem to be solved by the present invention may therefore be regarded as a provision of an alternative means for the oral delivery of 3-[(1 S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one.

The solution proposed in claims 1 and 12-13 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

It is generally known in the art that the liquid formulations comprising API, can be incorporated into an oral capsule for the oral delivery of the active ingredients - see D4-D6, which all disclose an oral capsule filled with the liquid composition comprising an active ingredient and Cremophor EL, PEG400 as the vehicle. Furthermore, even D1 (see [0305]) and D2 (see [0185]) itself suggest to incorporate the compound 67 in a form of a capsule.

Hence, the characterising features of claims 1 and 12-13, namely an oral capsule, would be regarded by the skilled man as being the result of normal development procedure and therefore, the solution proposed in claims 1 and 12-13 of the present application cannot be considered to involve an inventive step (Article 33(3) PCT).

6.2 Dependent claims 2-3, 5, 8-11 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step in the absence of a surprising technical effect brought about by the distinguishing technical features.

It is noted that in the present application there is no evidence (experimental comparative data) provided showing an unexpected, surprising effect coming from the specific pH modifier, specific salt or from the specific amount of the active agent.

It is considered that in the absence of any effect linked to such a feature over those known from the prior art, the single structural modification such as variation of the amount of the active agent, selection of a specific salt ora specific pH modifier belong to common experimental design that a skilled person would optimize in routine experiments. No inventive step (Article 33(3) PCT) would be acknowledged for claims 2-3, 5 and 8-11.

7 The subject-matter of claims 4, 6, 7, 14 meets the requirements of Article 33(3) PCT.

The subject-matter of claims 4, 6-7 and 14 differs from this known in D1 as the closest prior art inter alia in that a composition is in a form of capsule and further comprises an anhydrous pH modifier.

The composition in D1/D2 comprise a glycine-NaOH buffer that is not anhydrous.

There is no teaching available in the prior art that would prompt the skilled person to combine 3-[(1 S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one with an anhydrous pH modifier that would allow the incorporation of a solid, and not a liquid composition into a capsule.

Claims 4, 6-7 and 14 are thus allowable under Article 33(3) PCT.

8 The subject-matter of claim 15 and all dependent claims 16-29 referring back to claim 15, meets the requirements of Article 33(3) PCT.

The subject-matter of claim 15 differs from this known in D1 as the closest prior art inter alia in that a composition is not liquid but is in a form of spray-dried dispersion and contains PVP-VA and a specific pH modifier being different than glycine-NaOH buffer.

There is no teaching available in the prior art that would prompt the skilled person to combine 3-[(1 S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one with PVP-VA inorder to form a solid dispersion that is further combined with a specific pH modifier.

Claims 15-29 are thus allowable under Article 33(3) PCT.

Re Item VIII

Certain observations on the international application

9 The approximate term "about" used in claims 9-11, 15-27 leaves the reader in doubt as to the exact meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

10 Independent claim 15 and dependent claims 16-17, 20-27 contain the reference to "SDD".

Such a name "SDD" is vague and imprecise resulting in the lack of clarity of claims 16-17 and 20-27 (Article 6 PCT) when used to interpret them.

11 Present claims 26-27 relates to a product in a form of particles, wherein said particles are defined by the mean particle size, without indicating the measuring condition and equally important the calculation method.

The use of this parameter in the present context is considered to lead to a lack of clarity under Article 6 PCT, because the claims do not clearly identify the products (i.e. by mentioning in the claim the method used to obtain said particle diameter.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO/ISA)

General information

For all international applications, the competent International Searching Authority **(ISA)** will establish an international search report **(ISR)** accompanied by a written opinion of the International Searching Authority **(WO/ISA)**. The **WO/ISA** may be responded to by

- filing informal comments with the **International Bureau of WIPO (IB)** (where no demand for international preliminary examination **(demand)** is filed)
- filing amendments under Art. 19 PCT (this can be done whether or not a **demand** is filed)
- filing amendments under Art. 34 PCT and/or formal observations in response to objections raised in the **WO/ISA** (where a **demand** *is* actually filed)

This document explains these possibilities.

Filing informal comments

After receipt of the **ISR and WO/ISA**, the applicant may file informal comments on the **WO/ISA, directly with the IB** (see International Search and Preliminary Examination Guidelines 2.15). These will be communicated to the designated/elected Offices, together with the International Preliminary Report on Patentability **(IPRP)** at 30 months from the priority date.

Amending claims under Art. 19 PCT

The applicant may file **amended claims** under Art. 19 PCT, **directly with the IB** by the later of the following dates:

- 2 months from the date of mailing of the **ISR** and the **WO/ISA**
- 16 months from the priority date

However, any such amendment received by the **IB** after the expiration of the applicable time limit shall be **considered to have been received on time** by the **IB**, if it reaches it **before** the technical preparations for international publication have been completed (the 15th day prior to the date of publication, see PCT Applicant's Guide, International Phase, 9.013).

For further information, please see Rule 46 PCT as well as form PCT/ISA/220.

Please also note that, when filing amended claims under Art. 19 PCT, such amendments shall be **accompanied by a letter** identifying the amendments made and also the basis for the amendments in the application as originally filed (Rule 46.5(b) PCT). Where a **demand** is filed, failure to comply with this requirement may result in the amendments being ignored in the International Preliminary Examination Report **(IPER)**, see Rule 70.2(c-*bis*) PCT.

XS CPRTENFRDE

BNSDOCID: <XS 2006100103CF_I_>