

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/US2023/071721

International filing date (day/month/year)
04.08.2023

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International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/16 A61K9/14 A61K9/20 A61K31/404 A61K31/4439 A61K31/47 A61P11/00

Applicant
VERTEX PHARMACEUTICALS INCORPORATED

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
Gitschiner Str. 103
D-10958 Berlin
Tel. +49 30 25901 - 0
Fax: +49 30 25901 - 840

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-43(partially)

because:

☒ the said international application, or the said claims Nos. 1-43(partially) relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-43(partially) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☒ the claims, or said claims Nos. 1-43(partially) are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

see separate sheet

☒ no international search report has been established for the whole application or for said claims Nos. 1-43(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13~~ter~~.1(a).

☒ See Supplemental Box for further details

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>9-15, 17-19, 21-28, 33-38(all partially)</u>
	No: Claims	<u>1-8, 16, 20, 29-32, 39-43(all partially)</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-43(partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>1-43(partially)</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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 III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 Present independent claims 1, 24, 25, 26, 27, 28 relates to an extremely large number of possible compounds hidden by the names compound I, Compound II and Compound III. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds I, II and III claimed - see e.g. [009], [0053], [0054], [0058]-[0061] and examples 1-9, namely for:

- a Compound I being only N-(1,3-dimethylpyrazol-4-yl)sulfonyl-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide (also known as elexacaftor)

- a Compound II being only (R)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-N (1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropanecarboxamide (tezacaftor)

- a Compound III being only N (5-hydroxy-2,4-di-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (ivacaftor).

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1-42 (PCT Guidelines 9.19 and 9.23).

The search of claims 1-42 was thus restricted to those claimed compounds I, II, III, which appear to be supported, namely for the specific compounds I-III as mentioned above and defined in [0009], [0053], [0054], [0058]-[0061].

2 No opinion is formulated with respect to the subject-matter that is not covered by the search report (Rule 66.1(e) PCT).

Re Item V

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

3 Reference is made to the following documents:

D1 Anonymous: "HIGHLIGHTS OF PRESCRIBING INFORMATION - TRIKAFTA",
, 1 June 2021 (2021-06-01), pages 1-18, XP093100684,
Retrieved from the Internet:

URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212273s004lbl.pdf
[retrieved on 2023-11-13]

- D2 WO 2020/242935 A1
- D3 WO 2019/152940 A1
- D4 KAUSHIKA PATEL ET AL: "Solid dispersion technology as a formulation strategy for the fabrication of modified release dosage forms: A comprehensive review",
DARU JOURNAL OF PHARMACEUTICAL SCIENCES, BIOMED CENTRAL LTD, LONDON, UK,
vol. 30, no. 1, 18 April 2022 (2022-04-18), pages 165-189,
XP021302810,
DOI: 10.1007/S40199-022-00440-0
- D5 BHUJBAL SONAL V. ET AL: "Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies",
ACTA PHARMACEUTICA SINICA B,
vol. 11, no. 8, 1 August 2021 (2021-08-01), pages 2505-2536,
XP055881096,
ISSN: 2211-3835, DOI: 10.1016/j.apsb.2021.05.014

- 4 The relevant passages are those indicated in the search report, unless otherwise specified.
- 5 The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims 40-43 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.
- 6 In view of the lack of clarity (see objections under Box VIII) any statement of novelty and inventive step of claims 1-43 is difficult.

Hence, for the purpose of the present opinion the unclear features "Compound I Form A" and "substantially have been disregarded."
- 7 The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claims 1-8, 16, 20, 29-32 and 39-43 is not new.

7.1 Regarding claims 40-43 it should be noted that the discovery of a mechanism of action "CFTR-mediated disease" cannot render novel the known use of a compound in the treatment of a disease or pathological disorder.

7.2 D1 discloses a Trikafta® product comprising a tablet comprising a fixed-dose triple combination of elexacaftor (a compound I as presently defined in [0053]), tezacaftor (a compound II as presently defined in [0053] - see also example 5) and ivacaftor (a compound III as presently defined in [0053] - see also example 5) co-packed with ivacaftor tablets.

The elexacaftor, tezacaftor and ivacaftor fixed-dose combination tablets of D1 are available as: orange, capsule-shaped, film-coated tablet containing 100 mg of elexacaftor, 50 mg of tezacaftor, 75 mg of ivacaftor, or light-orange, capsule-shaped, film-coated tablet containing 50 mg of elexacaftor, 25 mg of tezacaftor, 37.5 mg of ivacaftor. The fixed-dose combination tablet contains the following inactive ingredients: hypromellose (solid dispersion component), hypromellose acetate succinate (solid dispersion component), sodium lauryl sulfate (solid dispersion component), croscarmellose sodium (disintegrant), microcrystalline cellulose (filler) and magnesium stearate (lubricant). The tablet film coat contains hypromellose, hydroxypropyl cellulose, titanium dioxide, talc (glidant), iron oxide yellow (sweetener) and iron oxide red. Trikafta is known in the art as being a marketed formulation based on solid dispersion technology (see D4-D5).

Hence, claims 1-8, 16, 20, 29-32 and 39-43 do not meet the requirements of novelty under Article 33(1) PCT.

8 The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of claims 1-43 does not involve an inventive step.

8.1 In view of their lack of novelty, claims 1-8, 16, 20, 30-32 and 39-43 lack inventive step (Article 33(3) PCT).

8.2 Dependent claims 9-15, 17-23, 33-38 and "pseudo "independent claims 24-28 (see objection below under point 13) 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 use of specific amount of active ingredient or form the use of specific excipients.

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 drug and excipients belong to common experimental design that a skilled person would optimise in routine experiments. No inventive step under Article 33(3) PCT is thus acknowledged for the subject-matter of claims 9-15, 17-28 and 33-38.

Re Item VII

Certain defects in the international application

- 9 The unit "torr" employed in [00166], [00177], [00183]-[00186] is not additionally expressed in terms of the units stipulated by Rule 10.1/(a)/and/(b) PCT.
- 10 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1-D3 is not mentioned in the description, nor is this document identified therein.

Re Item VIII

Certain observations on the international application

- 11 As mentioned under Item III, the terms Compound I, Compound II, Compound III of the present independent claims 1, 24, 25, 26, 27, 28 do not meet the requirements of Article 6 PCT, because they do not define the essential ingredients of the Claims. Only by reference to the description, it can be established what kind of structures are hidden by said names. By reference to the description, the claims lack thus clarity because the claims must define the scope for which protection is claimed by themselves.
- 12 Claims 2, 24-29, 32-34 relating to Compound I Form A are not sufficient to define the mentioned crystalline form A (Article 6 PCT) because they do not have a universally accepted meaning. The expressions "form A" as used in said claims can only make sense if they are accompanied by analytical data, for example the characterizing peak values of the XRPD of said form. At the moment, the expression "form A" is thus meaningless per se and current claims 2, 24-29, 32-34 are unclear.
- 13 Although claims 1, 24, 25, 26, 27, 28 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

It seems rather that the independent claims 24-28 comprise all the features of claim 1 and are therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

- 14 The term "substantially" used in claims 3-4, 9-10, 24-28, 30-34 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).
- 15 The approximate term "about" used in claims 9-10, 12, 14, 17, 19, 21, 23-39 and 42 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).
- 16 The acronyms "HPMCAS", "SLS", "HPMC" and "CFTR" used in claims 7-10, 24-28 and 40-41 do not fulfil the clarity requirements of Article 6 PCT. Such names "HPMCAS", "SLS", "HPMC" and "CFTR" are vague and imprecise resulting in the lack of clarity of claims 1-3 (Article 6 PCT) when used to interpret them.
- 17 The subject-matter of claims 40-43 does not meet the requirements of Article 6 PCT for the following reasons. The therapeutic application of the products is functionally defined by a mechanism of action, that is "CFTR-mediated disease", which does not allow any practical application in the form of a defined, real treatment of a pathological condition.
- 18 The vague and imprecise statements "and/or the like", "not limited to", "non-limiting" used throughout the description imply that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.
- 19 Anything in the description which is called an "Example" should be an embodiment of what is actually claimed. The current examples, e.g. examples 1-4, are not true examples that do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT