

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/US2018/036610	International filing date (day/month/year) 08.06.2018	Priority date (day/month/year) 08.06.2017
International Patent Classification (IPC) or both national classification and IPC INV. A61K31/4045 A61K31/443 A61K31/454 A61K31/47 A61P11/12		
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 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 Allnutt, Sarah 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. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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>1-62</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-62</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-62</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

1. Claims 1-62 relate to a subject-matter considered by this Authority to be covered by the provision 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.

2. The documents cited in the International Search Report are consecutively numbered D1-D4 in this communication; this numbering will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.

Novelty (Article 33(2) PCT)

3. The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-62 are new in the sense of Article 33(2) PCT.

WO2014014841 (D2) discloses the combination of compounds II and III for the treatment of patients with cystic fibrosis having a Phe508del CFTR mutation. No disclosure of compound I.

Wainwright et al (D3) discloses the combination of compounds IV and III for treatment of patients with cystic fibrosis having a Phe508del CFTR mutation. No disclosure of compound I.

Norman et al (D4) is an evaluation of selective CFTR modulators including compounds II, III and IV of the application. Combination of compounds is reported as providing additive effects and superior efficacy. No disclosure of compound I.

Inventive Step (Article 33(3) PCT)

5. The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-62 involve an inventive step in the sense of Article 33(3) PCT.

Either D2 or D3 could be taken as the closest prior art.

The subject matter of independent claims 1,51,53,54-59 differ in the additional combination with compound I.

The technical effect as demonstrated by the application in the examples is that compound I potentiated functional CFTR protein transport when combined with compound II and/or III (Example 7). Compound I in triple combination with compounds II and III, in patients heterozygous for F508del, resulted in statistically significant and clinically meaningful improvements in ppFEV₁ and sweat chloride (Example 8).

Thus the problem to be solved is "provision of a compound to improve treatment of cystic fibrosis"

None of the prior art documents disclose compound I of the application, it would appear at the time of priority that this compound was not in the public domain and therefore the skilled person could not have arrived at the specific compound I, let alone predict its activity as demonstrated.

Thus claims 1-62 fulfill the requirements for an inventive step in the sense of Article 33(3) PCT.

Re Item VI

Certain documents cited

6. Although D1 is not a document pursuant to Rule 64.1 PCT, it discloses compound I of the current application in various combinations with compounds II-IV.

It is noted that this document does not disclosed the specific dosage claimed for compound I.

This document may be taken into account in the regional phase for the assessment of inventive step should the priority be found invalid for the current application.