

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

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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/US2020/021648

International filing date (day/month/year)
09.03.2020

Priority date (day/month/year)
11.03.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/04

Applicant
PTC THERAPEUTICS, INC.

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:



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Date of completion of
this opinion

see form
PCT/ISA/210

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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 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	<u>1-18</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-18</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-18</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

- D1 WO 2014/081906 A1 (PTC THERAPEUTICS INC.) 30 May 2014
(2014-05-30)cited in the application
- D2 Y. HUANG ET. AL.: "Fundamental aspects of solid dispersion technology
for poorly soluble drugs.",
ACTA PHARMCEUTICAL SINICA,
vol. 4, no. 1, 1 January 2014 (2014-01-01), pages 18-25, XP055497465,
DOI: 10.1016/j.aspb.2013.11.001

Re Item V

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

D1 discloses the compound of claim 1 (page 146, compound 109). According to the description of the present application, the preparation of this compound gives the crystalline form.

The subject-matter of claim 1 therefore differs from this known compound in that the compound is amorphous, and is therefore new (Article 33(2) PCT).

The dependent claims 2 and 3 are novel by consequence.

Claims 4 and dependent claims 5 to 10 are drawn to solid dispersions comprising the amorphous form of claim 1, and are novel by consequence.

Claim 15 and dependent claims 16 to 17 are drawn to pharmaceutical compositions comprising the solid dispersions of claims 4 to 10 and are novel by consequence.

Claim 18 is drawn to a process for the preparation of a pharmaceutical composition according to claim 15 and is novel by consequence.

Claims 1 to 18 therefore meet the Novelty requirements of Article 33(2) PCT.

The problem to be solved by the present invention may be regarded as the provision of compound 109 of D1 in a form with improved solubility and bioavailability.

The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

D1 contains no information on how to prepare compound 109 in an amorphous form.

The preparation of solid dispersions of poorly soluble API compounds is discussed in D2. However, even by combining D1 and D2, the skilled person would not expect that the preparation of an amorphous form of compound 109 of D1 using the solid dispersion technique would inevitably result in a form of compound 109 having improved bioavailability. The examples of the description show that the problem underlying the present application has been solved, and the results could only have been arrived at by experimentation.

- 1 Since claim 1 meets the requirements of Article 33(2) PCT, the dependent claims 2 and 3, as well as claims 4 to 10 drawn to solid dispersions comprising the amorphous form of claim 1, claims 11 to 14 drawn to processes for the preparation of the solid dispersions, claims 15 to 17 drawn to pharmaceutical compositions comprising the solid dispersions, and claim 18 drawn to a process for the preparation of the pharmaceutical compositions also meet the requirements of Article 33(3) by consequence.