

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/US2020/049487	International filing date (day/month/year) 04.09.2020	Priority date (day/month/year) 06.09.2019
International Patent Classification (IPC) or both national classification and IPC INV. C07D413/14 C07D413/12 A61P37/00 A61K31/553		
Applicant RIGEL PHARMACEUTICALS, 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:  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 Lauro, Paola 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	
	No: Claims	<u>1-43</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-43</u>
Industrial applicability (IA)	Yes: Claims	<u>1-43</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

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

1 **Re Item V**

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

1.1 Reference is made to the following documents:

- D1 WO 2014/125444 A1 (GLAXOSMITHKLINE IP DEV LTD [GB]) 21 August 2014 (2014-08-21) cited in the application
- D2 WO 2016/027253 A1 (GLAXOSMITHKLINE IP DEV LTD [GB]) 25 February 2016 (2016-02-25)
- D3 WO 2017/136727 A2 (DENALI THERAPEUTICS INC [US]) 10 August 2017 (2017-08-10)
- D4 WO 2018/154520 A1 (GLAXOSMITHKLINE IP DEV LTD [GB]) 30 August 2018 (2018-08-30)
- D5 PHILIP A. HARRIS ET AL: "DNA-Encoded Library Screening Identifies Benzo[b][1,4]oxazepin-4-ones as Highly Potent and Monoselective Receptor Interacting Protein 1 Kinase Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, vol. 59, no. 5, 10 March 2016 (2016-03-10), pages 2163-2178, XP055302242, US
ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.5b01898
- D6 PHILIP A. HARRIS ET AL: "Identification of a RIP1 Kinase Inhibitor Clinical Candidate (GSK3145095) for the Treatment of Pancreatic Cancer", ACS MEDICINAL CHEMISTRY LETTERS, vol. 10, no. 6, 9 May 2019 (2019-05-09), pages 857-862, XP055651088, US
ISSN: 1948-5875, DOI: 10.1021/acsmchemlett.9b00108

- 1.2 Claims 35-43 relate to subject-matter considered by this Authority to be covered by the provisions 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.

- 1.3 Current claim 8 lists seems to refer to compounds which are meant to be disclaimed from claim 1; however, claim 1 has no limitation, therefore, the definition as given in claim 1 has been taken into account for the examination. In addition, in view of the number of compounds listed in claim 8, when the limitation is applied to claim 1, it is completely unclear what is the remaining subject-matter of claim 1 (Article 6 PCT).

1.4 **Novelty**

D1 to D4 (see details in the ISR) disclose compounds which fall within the definition of formula (I). The subject-matter of claim 1 and dependent claims referring to more specific embodiments is thus not novel. It appears that compounds carrying R1 selected from the list given in claim 27 are novel. If the listed compounds in claim 28 all carry such substituent R1, then they would appear to be novel. Since the compounds disclosed in D1 to D4 possess the same qualitative activity as the current compounds, also the subject-matter of claims 33-43 is considered to be anticipated (Art. 33(2) PCT).

1.5 **Inventive step**

The following comments refer to the subject-matter considered to be novel, namely the subject-matter of claims 27-43.

- 1.6 The problem underlying the present application appears to reside in the provision of compounds as RIP1 Kinase Inhibitors. The solution is provided by benzo-oxa-azepinone derivatives. D1 to D6 disclose compounds with the same activity. The difference re D1 to D6 would reside in the nature of the substituent on ring A (i.e. R1). However, starting from D1, which discloses a general formula which includes a variety of substituents for the ring corresponding to A, the skilled person would take the teaching that the substituent may be varied without the activity being affected. Therefore, since the current substituents R1 are seen as obvious modifications of the substituents listed for formula (I) in D1, the provision of the current compounds as alternative RIP1 Kinase Inhibitors is considered to be obvious. If the problem is to be reformulated as the provision of compounds with unexpected activity compared to the structurally closest compound of the prior art, in the absence of data it is not yet known if such a

problem is solved. In this connection, it is noted that a comparative test is included in the description of the present application; however, since the comparative compound is a benzo-oxazepinone which carries no substituent on the ring corresponding to A, it is not to be taken as the structurally closest compound of the prior art.

2 **Re Item VI**

Certain documents cited

The following documents:

- D7 WO 2019/213447 A1 (RIGEL PHARMACEUTICALS INC [US]) 7 November 2019 (2019-11-07)
- D8 WO 2019/213445 A1 (RIGEL PHARMACEUTICALS INC [US]) 7 November 2019 (2019-11-07)

have been published after the priority date of the current application and it is therefore not taken into account for the purpose of the present opinion.

3 **Re Item VII**

Certain defects in the international application

- 3.1 Ring A is not defined in the claims.
- 3.2 Current claim 8 lists seems to refer to compounds which are meant to be disclaimed from claim 1; however, claim 1 has no limitation. In view of the number of compounds listed in claim 8, when the limitation is applied to claim 1, it is completely unclear what is the remaining subject-matter of claim 1 (Article 6 PCT).