

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/SA/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/B2022/059630

International filing date (day/month/year)
07.10.2022

Priority date (day/month/year)
08.10.2021

International Patent Classification (IPC) or both national classification and IPC
 INV. A61P35/00 C07D471/04 A61K31/5377 A61K31/496 A61K31/4545 A61K31/4375

Applicant
VRISE 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 43 <i>bis</i> .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 66.1 *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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.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. 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>13, 17-20, 27, 35, 40-53, 61-66</u>
	No: Claims	<u>1-12, 14-16, 21-26, 28-34, 36-39, 54-60</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-66</u>
Industrial applicability (IA)	Yes: Claims	<u>1-66</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. 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.

Reference is made to the following documents:

- D1 DATABASE REGISTRY [Online]
 CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 16 January
 2002 (2002-01-16), 15 January 2002 (2002-01-15), 27 November 2001
 (2001-11-27) 2x, 19 November 2001 (2001-11-19), 9 November 2001
 (2001-11-09), 9 November 2001 (2001-11-09), 29 August 2001
 (2001-08-29), 14 November 2000 (2000-11-14), 2 November 2000
 (2000-11-02), 1 November 2000 (2000-11-01), 31 October 2000
 (2000-10-31), respectively for the following
 Database accession no. 3833406-08-4, 383160-52-9, 371937-38-1,
 371932-32-0, 370873-79-3, 368434-58-6, 368433-30-1, 353487-11-3,
 302785-61-1, 300835-88-5, 300732-64-3, 300590-05-0
- D2 WO 2005/087767 A1 (MERCK & CO INC [US]; HAN WEI [US] ET AL.) 22
 September 2005 (2005-09-22)
- D3 US 2005/277643 A1 (KELLY MICHAEL G [US] ET AL) 15 December 2005
 (2005-12-15)
- D4 WO 2012/058173 A1 (MERCK SHARP & DOHME [US]; MERCK CANADA
 INC [CA] ET AL.) 3 May 2012 (2012-05-03)
- D5 WO 2020/239077 A1 (SHANGHAI HANSOH BIOMEDICAL CO LTD [CN]
 ET AL.) 3 December 2020 (2020-12-03)
- D6 WO 2018/140600 A1 (ARAXES PHARMA LLC [US]) 2 August 2018
 (2018-08-02)

Claims 55-58 and 60-66 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.

Novelty

Current formula (A) may be considered to be a novel selection from the general disclosures of D5 and D6. However, D2-D4 disclose general formulae overlapping with the current general formula plus D1-D4 disclose specific compounds falling within current formula (A) (see citations given in the international search report). Moreover, D2 and D3 disclose pharmaceutical compositions comprising the same (see D2 claim 9 and D3 claim 100) and D3 additionally discloses the use thereof in the treatment of cancer (see D3 claim 110). Novelty in the sense of Article 33(2) PCT of the compounds of current formula (A), pharmaceutical compositions comprising the same plus the said compounds or compositions for use in treating cancer thus remains to be established.

Inventive Step

D5 and D6 both disclose naphthyridine derivatives which by way of inhibiting KRAS G12 mutations are useful for the treatment of in particular various cancer types such as e.g. lung cancer. D5 is currently considered to represent the closest prior art.

Compounds of current formula (A) generically overlap with the general formula (I) of D5 and are considered to be a novel selection therefrom, essentially due to the current core heterobicycle wherein the parameters X^{1-3} of D5 are chosen to be as follows: X^1 is carbon, X^2 is nitrogen and, in particular, X^3 is carbon substituted by current substituent R. In contrast thereto, the closest compounds of D5 contain as said X^3 group a nitrogen atom (see e.g. formulae (III)-(VI) and examples 1-20 of D5). The current compounds have been shown to have the desired activity (see current tables 4-7; please note that the nature of the representative "compound A" in tables 5-7 is not clear). No unexpected improved effect has been shown to be due to the essential difference to the closest prior art. As a consequence, the current compounds are considered to solve the less-ambitiously formulated problem of providing further naphthyridine derivatives which inhibit KRAS G12 mutations and are thus useful for the treatment of cancer.

D5 and D6 disclose the qualitative interchangeability of said nitrogen of the closest specific prior art compounds and a (substituted) carbon atom (see D5 claim 1 wherein X^3 can be a nitrogen or a carbon atom, optionally substituted by e.g. cyano group; see D6 claim 1, in particular the definitions of W, X, Y and Z therein), i.e. both prior art documents generically encompass compounds having the current core heterobicycle with X^3 being a carbon atom substituted by current group R. The skilled person looking for a solution to the given problem therefore didn't have to involve any inventive effort to consider the current compounds as alternatives having the desired activity. An inventive

step in the sense of Article 33(3) PCT could therefore only be acknowledged for those well-delimited current compounds which solve the problem of providing unexpectedly improved anticancer agents which inhibit KRAS G12 mutations. A surprising technical effect re the closest prior art, however, remains to be elucidated.

Re Item VI.

Certain documents cited

Certain published documents

Application No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (day/month/ year)
D7: WO 2021/219072 A1	04-11-2021	29-04-2021	30-04-2020 22-12-2020

D7 discloses a general formula overlapping with the current general formula (see in particular formula I-6 of D7), from which the overlapping current scope may be considered to be a novel selection, essentially due to the nature of current group "R".

D7 has been filed prior to the currently claimed priority dates (08.10.2021 and 10.02.2022), and published in-between the said currently claimed priority dates. As a consequence, it may be relevant for the assessment of novelty and inventive step for the current subject-matter not entitled to the first claimed priority date, and for novelty for the current subject-matter entitled to the first claimed priority date.

Re Item VIII.

Current claim 1 is considered not to be clearly defined (Article 6 PCT):

- First of all, it relates (the same as claims 2 and 30) to "prodrugs". This term is a functional definition which attempts to define a chemical compound in terms of a result to be achieved without proven general knowledge to show which derivatives in this specific case are suitable prodrugs. The term could even be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable variants. In such a situation, when the invention cannot be carried out

over the whole claimed area without imposing an undue burden on the skilled person, the disclosure may be considered insufficient, even when simple in vivo or in vitro tests are available to determine whether or not a particular compound is covered by the claims. As a consequence, only phosphate or boronic esters of hydroxy groups as disclosed on current page 49 are currently considered. Claim 1 should be reformulated accordingly.

- The definition of "E" being "a group capable of forming a covalent bond or an "Electrophile" or "electrophilic moiety capable of forming a covalent bond" is not clear and, as regards the ability to form a covalent bond, defined by a result-to-be achieved. At present, all chemical groups and atoms which are potentially able to form a covalent bond, e.g. hydrogen atoms, are considered to be encompassed by said group E whenever not further defined (also e.g. in claim 16).
- R or R¹ being bound via group R^b does not make sense whenever R^b stands for a hydrogen atom.
- On page 3 of the claims a substituent R^y has been defined although said substituent appears not to be present in claim 1. The definition should therefore be deleted.
- According to page 43, the definition of "alkoxy" includes cyclic alkoxy groups. This goes beyond the general understanding of the said term. It is noted that, as is common practice, alkyl groups are defined to be hydrocarbon chains (see page 42). If alkoxy is indeed intended to include cycloalkoxy groups this should be made clear in the claim itself.

Claims 2, 3 and 41-53 are drafted as independent claims although they relate to dependent subject-matter. The said claims should therefore be drafted as dependent claims, as appropriate.

In claim 30, X² potentially stands for CH₂-E, which, however, is not possible as it would result in the carbon having five bonds.

In claim 31, A¹ potentially stands for methyl. In this case, apparently, a methylene group is intended instead.

Additionally, it is noted that D3 and D5-D7 are not yet cited and briefly discussed and that the description contains incorporations by reference (such as on pages 1 or 42) and contains a paragraph relating to the "general concept of the invention" (see p.113).