

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/IB2022/053285

International filing date (day/month/year)
07.04.2022

Priority date (day/month/year)
08.04.2021

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/12

Applicant
VAXTHERA SAS

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
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Montero Lopez, B

Telephone No. +31 70 340-0



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 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 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>7, 15-29, 31-36, 44-49, 53-56, 59-68, 71-76, 79, 80, 83, 84, 87, 88, 91-94, 97-104, 107, 108, 111-114, 118, 122, 125-131, 134-137, 140-146, 148-151, 154, 155, 158-162, 182-192</u>
	No: Claims	<u>1-6, 8-14, 30, 37-43, 50-52, 57, 58, 69, 70, 77, 78, 81, 82, 85, 86, 89, 90, 95, 96, 105, 106, 109, 110, 115-117, 119-121, 123, 124, 132, 133, 138, 139, 147, 152, 153, 156, 157, 163-181</u>
Inventive step (IS)	Yes: Claims	<u>15, 19-29, 146, 149, 150</u>
	No: Claims	<u>1-14, 16-18, 30-145, 147, 148, 151-192</u>
Industrial applicability (IA)	Yes: Claims	<u>1-192</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 V

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

Claims 163-181 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.

Patentability, in particular novelty and inventive step, of claims 163-181 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the composition.

Reference is made to the following documents:

- D1 US 2017/096455 A1 (BARIC RALPH [US] ET AL) 6 April 2017
(2017-04-06)
 - D2 CN 111 533 790 A (UNIV SUN YAT SEN) 14 August 2020 (2020-08-14)
 - D3 AHAMMAD ISHTIAQUE ET AL: "Designing a novel mRNA vaccine against SARS-CoV-2: An immunoinformatics approach",
INTERNATIONAL JOURNAL OF BIOLOGICAL MACROMOLECULES,
ELSEVIER BV, NL,
vol. 162, 26 June 2020 (2020-06-26), pages 820-837, XP086280657,
ISSN: 0141-8130, DOI: 10.1016/J.IJBIOMAC.2020.06.213
[retrieved on 2020-06-26]
- 1 Claims 1-18 are directed to a nucleic acid construct comprising one to three nucleic acid sequences encoding a mosaic coronavirus Spike protein or antigenic fragment, optimized for maximum T cell epitope coverage of at least two human coronaviruses. Claims 30-37, 115-118, 159-181 involve pharmaceutical compositions, host cells and vectors, kits and medical uses.

1.1

- 2 Claims 19-29 are directed to various combinations of coronavirus Spike sequences.
- 3 Claims 38-114 relate to a coronavirus vaccine vector comprising at least a polynucleotide encoding a Coronavirus mosaic S protein or antigenic fragment optimized for maximum T cell epitope coverage of at least two human coronavirus.
- 4 Claims 119-158 relate to a coronavirus vaccine comprising a spike mosaic protein or antigenic fragment, optimized for maximum T cell epitope coverage of at least two human coronaviruses.
- 5 Claims 182-192 involve a lipid nanoparticle mRNA composition encoding a mosaic spike sequence.
- 6 The subject-matter of various independent claims is defined in terms of a result-to-be-achieved feature, i.e. "optimized for maximum T cell epitope coverage", where this feature in itself also involves ambiguous, relative terms such as "optimized" and "maximum". Due to the inherent unclarity of this feature, the claims are considered to encompass a sequence comprising T cell epitopes of at least two human coronaviruses.
- 7 Document D1 refers to various human coronavirus, i.e. 229E, OC43, NL63, HKU1, SARS and MERS (page 1, [0005]) and discloses a chimeric (mosaic) spike protein comprising regions of two different coronavirus (page 1, [0007]), a nucleic acid and vector ([0008]). The chimeric spike antigen HKU3-Smix has components from HKU3, SARS and 279S (page 2, [0014]; figure 2; page 3, [0026]; figure 14) and protects against SARS challenge ([0017]; figure 5). The spike protein may comprise regions from three different coronavirus (page 4, [0035]). The chimeric protein or nucleic acid can be administered to a subject in a pharmaceutical composition (page 16, [0102] - page 17, [0105]).
- 7.1 Claims 1-6, 30, 37-43, 115-117, 119-121, 123, 124, 156, 157 and 163-181, are not novel and do not comply with the requirements of Article 33(2) PCT.
- 8 Document D2 discloses coronavirus mosaic antigen constituted by T cell epitopes selected by high frequency (abstract; page 4, [0007] - page 5, [0012]), in a combination of S, M, N or E protein from various coronavirus, i.e. NL63, 229e, OC43, HKU1, SARS, MERS, SARS-Cov2 (page 5, [0013]-[0015]). The antigen is provided in an adenovirus vector as a universal coronavirus vaccine (page 9, [0070] - page 10, [0075]). The examples show how to provide a mosaic

- S protein sequence expressed by a vector. In D2, SEQ ID NO:1 is 99.9% identical to claimed SEQ ID NO:1; SEQ ID NO:4 is 100% identical to claimed SEQ ID NO:3 and SEQ ID NO:3 is 99.9% identical to claimed SEQ ID NO:5
- 8.1 Claims 1-6, 8-14, 30, 37-43, 50-52, 57, 58, 69, 70, 77, 78, 81, 82, 85, 86, 89, 90, 95, 96, 105, 106, 109, 110, 115, 119-121, 123, 124, 132, 133, 138, 139, 147, 152, 153, 163-167, 170-181 are not novel and do not comply with the requirements of Article 33(2) PCT.
- 9 Claims 7, 44, 122, 125 refer to a combination of sequences from more than three coronaviruses. The skilled person, from the teaching of D1 or D2, can extend the coverage to more than three coronavirus without the need of applying inventive skills. Claims 7, 44, 122, 125 are not inventive and do not comply with the requirements of Article 33(3) PCT.
- 10 Furthermore, the skilled person can select appropriate promoters, vectors and host cells as a routine method. Claims 16-18, 31-36, 113, 114, 118, 158 do not involve an inventive step and do not comply with the requirements of Article 33(3) PCT.
- 11 Analogously, the provision of a kit is a routine procedure for the skilled person. Claims 159-162 do not comply with the inventive step requirements of Article 33(3) PCT.
- 12 Claims 45-50, 53-56, 59-68, 71-76, 79, 80, 83, 84, 87, 88, 91-94, 97-104, 107, 108, 111, 112, 126-131, 134-137, 140-145, 148-151, 154, 155 involve the presence of further second and third mosaic spike sequences. The skilled person would consider the possibility of adding further mosaic sequences to the constructs of D1 or D2 without the need of applying inventive skills. Claims 45-50, 53-56, 59-68, 71-76, 79, 80, 83, 84, 87, 88, 91-94, 97-104, 107, 108, 111, 112, 126-131, 134-137, 140-145, 148-151, 154, 155 do not comply with the requirements of Article 33(3) PCT.
- 13 Claims 19-29 are directed to various combinations of coronavirus Spike sequences. and are novel in accordance with Article 33(2) PCT.
- 13.1 These specific combinations are not suggested in the prior art and involve an inventive step in accordance with Article 33(3) PCT.
- 14 Claims 182-192 involve a lipid nanoparticle mRNA composition encoding a mosaic spike sequence and are a novel in accordance with the requirements of Article 33(2) PCT.

- 14.1 However, mRNA lipid nanoparticle Coronavirus spike vaccines are already known in the art; Document D3 discloses such a vaccine for a multiepitopic spike sequence (abstract; page 821, col. right, par. 2-4). It would be obvious for the skilled person that the construct of D2 could also be provided as a mRNA vaccine in accordance with D3. Claims 182-192 do not involve an inventive step and do not comply with the requirements of Article 33(3) PCT.

Re Item VII

Certain defects in the international application

- 1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 and D2 is not mentioned in the description, nor are these documents identified therein.
- 2 The vague and imprecise statements in the description on page 155 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.
- 3 The term "sequence identity" is erroneously repeated in claim 10.
- 4 The features of a sequence between brackets in claims 17, 22, 23, 28, 29, 114 are considered optional.

Re Item VIII

Certain observations on the international application

- 1 The term "mosaic" used in the claims has no unambiguous meaning in the art 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 the claims unclear, Article 6 PCT.
- 2 The claims do not meet the requirements of Article 6 PCT because the matter for which protection is sought is not clearly defined. Various independent claims attempt to define the subject-matter in terms of the result to be achieved, i.e. "optimized for maximum T cell epitope coverage", which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

- 3 The relative terms "optimized" and "maximum" used in the claims have no well-recognized meaning and leave the reader in doubt as to the meaning of the technical feature to which they refer, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.
- 4 Claims 5, 6, 42, 43, 49, 123, 127 are inconsistent with independent claims 1, 38, 119 in the sense that they require optimization of epitope coverage for bat coronaviruses, while the independent claims from which they depend refer to human coronaviruses.
- 5 The term "newly emergent coronavirus" in claims 169, 172, 175 is vague and unclear and does not comply with the requirements of Article 6 PCT.