

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/IB2023/055592

International filing date (day/month/year)
31.05.2023

Priority date (day/month/year)
31.05.2022

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/22 A61P11/00 A61P9/00

Applicant
PFIZER 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

Authorized Officer

Covone-van Hees, M

Telephone No. -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.
 - 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. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 28-40(completely); 1-27, 41-75(partially)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 28-40(completely); 1-27, 41-75(partially) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ the claims, or said claims Nos. 28-40(completely); 1-27, 41-75(partially) are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13~~ter~~.1(a).
- ☒ See Supplemental Box for further details

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>1-27, 41-75(all partially)</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-27, 41-75(all partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>1-27, 41-75(all partially)</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 III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

- 1 The present application contains 11 independent claims defining the antibodies by reference to the (partial sequences of the) CDRs, VH/VL, HC/LC or plasmid encoding the VH/VL. There is no clear distinction between the independent claims because of overlapping scope. There are so many claims, and they are drafted in such a way that the claims as a whole are not in compliance with the provisions of clarity and conciseness of Article 6 PCT, as it is particularly burdensome for a skilled person to establish the subject-matter for which protection is sought. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search (PCT Guidelines 9.19 and 9.25).
- 1.1 Since the three CDRs of each of the variable domains of the light and heavy chains of an IgG are normally responsible for binding to the antigen, the IgG, in order to be uniquely defined by its structure only and have its characteristic binding specificity, needs to be defined by the number of CDRs required for its binding to fulfil the requirements of 6 PCT.
- 1.2 Additionally, in view of the available prior art, disclosing anti-BMP9 antibodies and the different properties of the exemplified antibodies, it is not clear what is the common novel and inventive technical feature(s). A formal non-unity may be raised in the regional phase.
- 1.3 The search was based on the subject-matter that, as far as can be understood, could reasonably be expected to be claimed later in the procedure, and the corresponding claims, namely claims 2 ii-ix and 4 defining the antibodies by the 6 CDRs. Accordingly independent claims referring to the antibodies defined by VH and VL or HC and LC are also covered by the search.
- 2 Additionally claims 28-40 define the antibody by reference to the binding residues. This definition is highly unclear and requires an undue burden to test and reproduce antibodies binding to the same residues. Additionally, due to the use of an unusual parameter to define the antibodies, a meaningful comparison with the prior art is not possible. The claims therefore lack clarity, support and disclosure to such an extent that they are not searched.

Re Item V

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

3 Cited documents

D1: US 2014/056902

D2: JP 2017 025011

D3: Tu Ly ET AL: (2019), XP055834375

D4: AYUMI SEKINE ET AL: (2017), XP009529612

3.1 Content of the cited documents

D1 and D2: produce neutralising murine anti-BMP9 (see whole doc).

D3 and D4 inhibit BMP9 with neutralising anti-BMP9 antibodies to treat PAH. The sequence of the antibodies are not disclosed in the documents (see the whole doc).

4 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 claim(s) 67-71, 74, 75 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

5 Novelty and Inventive Step (Art.33(2) PCT and Art.33(3) PCT)

5.1 Assessment of novelty and inventive step is done taken into account the limitation of search as explained under item III.

5.2 None of the available prior art documents discloses the CDRs or VH/VL claimed, accordingly claims 1-27, 41-75 are novel (Art.33(2) PCT).

5.3 Either D1 or D2 can be taken as closest prior art. Claims 2 and 4 differ over this disclosure by the nature of the sequences defining the CDRs of the antibody. Since no effect has been disclosed as associated with this difference, the problem addressed is defined as how to provide further antibodies binding BMP9. Given that the production of alternative antibodies to those known in the art is routine, the claimed subject-matter lacks inventive step.

- 5.4 Remaining claims do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step: they are mainly standard alternatives in this technical field, which fall within the routine skills of those in the art, and which do not appear to lead to any surprising effects or advantages. Indeed, the use of neutralising antibodies binding to BMP9 to treat PAH is known from D3 and D4.
- 5.5 However, the specific antibodies Ab1076 and Ab732 have been shown in mouse model to effectively treat PAH. While the provision of alternative antibodies is obvious, the provision of antibodies actually showing a potential therapeutic effect is unexpected and would be inventive.

Re Item VII

Certain defects in the international application

- 6 Dependency of claims 5-9 should be checked and corrected, since it makes no sense that these claims depend on claim 4.
- 7 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1-D4 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

- 8 If an IgG is defined by fewer than the six sequences of its CDRs, the claim will be objected to under Art.6 PCT as a general rule, antibodies need a VH and a VL domain or at least the 3 CDRs of the VH domain and the 3 CDRs of the VL domain for specific antigen binding. The exceptions to this general rule include: camelid, shark or camelised antibodies which are devoid of light chains or engineered single-domain antibodies (sdAbs) derived from heavy-chain antibodies. Therefore, a claim defining an antibody based on only the VH or VL region or on less than 6 CDRs lacks essential technical features. It should also be borne in mind that the lack of essential technical features leads to a lack of inventive step because, usually, the application does not provide any evidence showing that the presence of only a VH or VL chain or of less than 6 CDRs is sufficient to confer antigen binding and to attain the inventive technical effect shown for the entire antibody.