

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/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/EP2022/087260

International filing date (day/month/year)
21.12.2022

Priority date (day/month/year)
22.12.2021

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/18 A61P27/02

Applicant
CDR-LIFE AG

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. 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, 2, 4-6, 9-11, 39</u>
	No: Claims	<u>3, 7, 8, 12-38, 40-43</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. 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

1 Re item V

Reference is made to the following documents:

- D1 WO 2019/195136 A1 (NGM BIOPHARMACEUTICALS INC [US]) 10 October 2019 (2019-10-10)
- D2 WO 2021/226442 A2 (NGM BIOPHARMACEUTICALS INC [US]) 11 November 2021 (2021-11-11)
- D3 WO 2021/159946 A1 (BEIJING COMPLEMENT THERAPEUTICS LTD [CN]) 19 August 2021 (2021-08-19)

2 Articles 33(2) and 33(3) PCT

- 2.1 Document D1 and D2 teach antibodies to human complement C3 and their use to treat not only ocular diseases/disorders such as aged-related macular degeneration (AMD) and geographic atrophy (GA; cf. D1, examples) but also respiratory diseases such as severe respiratory disease (cf. D2, examples). In both cases, the aforementioned documents disclose selected antibody Hz38G19, a humanised monoclonal IgG2a anti-C3 antibody which is shown to inhibit the classical and alternative pathways of complement activation (cf. D1, D2 examples). Moreover, said antibody cross-reacts with cynomolgus monkey C3 with high affinities while also inhibiting complement activation. Additionally, the antibody is shown to have increased half-live properties as well as increased stability (cf. D1, D2 examples).
- 2.2 D3 discloses antagonist anti-C3 single chain monoclonal antibodies and their use to treat autoimmune diseases e.g. lupus erythematosus (cf. D3 examples).
- 2.3 Such is the scope of claim 3, which allows for up to 20% amino acid variation in the recited sequences, that without evidence to the contrary, the available prior-art is deemed to destroy novelty of such a broad claim (Article 33(2) PCT). Therefore claim 3 but also dependent claims 7, 8, 12-26, 33-38 and 40-43 is not considered to meet the requirements of Article 33(2) PCT. In view of the above, D1 is further deemed to destroy novelty of dependent claims 27-38 and 40-43 (Article 33(2) PCT).
- 2.4 None of the prior-art documents mentioned herein above appear to disclose such antibodies having the sequences recited in claims 1, 2, 4-6, 9-11 and 39. Therefore, said claims appear to fulfill the requirements of Article 33(2) PCT.

- 2.5 Should the applicant overcome the objection on novelty raised below, the subject-matter of claim 3, as presently formulated, would not contain an inventive step over the cited prior art. Moreover, in view of the prior-art documents at hand, claims 1, 2 and 4-43 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 since these additional features appear conventional and do not result in any unexpected technical effect (Article 33(3) PCT).
- 2.6 Document D1 can be considered as the closest prior art for the present set of claims 1-43.
- 2.7 The subject-matter of claims 1-43 differs from that of the content of D1 by the particular amino acid sequences recited in said claims.
- 2.8 However, since the antibodies of the present claim set only appear to define partial antibody sequences i.e. mixtures of 6 CDR sequences or VH/VL pairs containing up to 20% amino acid variation, and not complete well defined IgG antibodies as is the case in the examples of the application, in absence of proof of the contrary the application is mute as to a potential technical effect resulting from these sequences alone.
- 2.9 Indeed, it is noted that none of the antibodies of the present claims have quantitatively the technical features of the corresponding antibodies of the examples of the present application since it is well known in the field that such technical features are not inherent to the above mentioned partially defined antibodies especially those solely defined merely by 6 CDR sequences.
- 2.10 Therefore, at present, in view of the closest prior art, as well as the present scope of the claims 1-43, the objective technical problem to be solved can be seen in the provision of an alternative anti-C3 antibodies.
- 2.11 The solution to said objective technical problem, i.e., the subject-matter of claims 1-43, is not considered inventive for the following reasons:
- 2.12 The production and selection of monoclonal antagonist antibodies directed against well known proteins such as C3 is considered routine experimentation for the person skilled in the art as can be seen from the available prior-art documents D1-D3 listed and referred to herein above.
- 2.13 Similarly, the production of chimeric or humanised forms of such antibodies is also considered routine experimentation and cannot serve as a basis for inventive step.

- 2.14 Additionally, in view of aforementioned arguments, since the antibodies as recited in present claims 1-43 do not appear to solve an unforeseeable technical problem in the art or to lead to a specific technical effect over that already disclosed in D1, an inventive step cannot be acknowledged contrary to the requirements of Article 33(3) PCT.
- 2.15 Thus, following the above argumentation, inventive step cannot be acknowledged for claims 1-43 (Article 33(3) PCT).

Article 33(4) PCT

- 2.16 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.
- 2.17 Patentability, in particular novelty and inventive step of said claims has been assessed on the basis of a purpose-limited product taking into account the alleged effects of the substance or composition.

3 Re item VIII

Articles 6 and 5 PCT

- 3.1 The present claim set lacks clarity (Article 6 PCT) because a claim related to an antibody should contain **all** the characteristic features allowing the skilled person to identify which antibody fall within its scope (Articles 6 and 5 PCT).
- 3.2 It is noted that while an antibody defined by at least 6 CDRs, in a precise order on two distinct polypeptide chains (i.e. the light and the heavy chains), is the **minimum requirement** in order for the antibody to **at least bind** its target, the 6 CDRs alone, or even partially defined VH/VL sequences void of their particular Fc constant domain, may not be necessarily enough to insure that the technical effect in question is present e.g. the antibody's final affinity, inhibition, stability and/or production yield.
- 3.3 Therefore, in view of the above, the scope of the present claims is such that, at present, they encompass partially defined anti-C3 antibodies some of which may not even bind to the target epitope let alone, as previously explained, have a surprising technical effect over the antibodies of the prior-art.

- 3.4 Since the application does not plausibly show that all of the possible antibodies encompassed within the claims provide at least sufficient ligand specificity let alone a technical effect over the prior-art antibodies, the skilled person would not know which antibodies of this type would be useful for the invention and would therefore not be able to carry out the invention over the whole scope (Article 5 PCT).
- 3.5 Again, and importantly, it is noted that that none of the antibodies of the present claims have quantitatively the technical features of the corresponding antibodies of the examples of the present application since it is well known in the field that such technical features are not inherent to partially defined antibodies especially those solely defined by 6 CDR sequences.