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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2024/050407	09.01.2024	09.01.2023

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/18 A61P25/28 ADD. A61K39/00

Applicant
ALCHEMAB THERAPEUTICS LTD

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*bis*.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 notifed 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:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Gruber, Andreas 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 43*bis*.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 13*ter*.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 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-36, 39, 40, 42
	No:	Claims	1, 37, 38, 41
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-42
Industrial applicability (IA)	Yes:	Claims	1-42
	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

Reference is made to the following documents:

D1 F Mille ET AL: "Interfering with multimerization of netrin-1 receptors triggers tumor cell death",
Cell Death & Differentiation,
vol. 16, no. 10, 19 June 2009 (2009-06-19), pages 1344-1351, XP055219239,
GB
ISSN: 1350-9047, DOI: 10.1038/cdd.2009.75

D2 WO 2017/076864 A1 (NETRIS PHARMA [FR]) 11 May 2017 (2017-05-11)

D3 Guiqin Chen: "Netrin-1 receptor UNC5C cleavage by active [delta]-secretase enhances neurodegeneration, promoting Alzheimer's disease pathologies",
SCIENCE ADVANCES,
vol. 7, no. 16, 16 April 2021 (2021-04-16), XP093154734,
US
ISSN: 2375-2548, DOI: 10.1126/sciadv.abe4499
Retrieved from the Internet:
URL:https://www.science.org/doi/pdf/10.1126/sciadv.abe4499

D4 WO 2013/071119 A2 (GENENTECH INC [US]; HOFFMANN LA ROCHE [CH]) 16 May 2013 (2013-05-16)

D5 P R Spilman: "Netrin-1 Interrupts Amyloid-[beta] Amplification, Increases sA[beta]PP[alpha] in vitro and in vivo, and Improves Cognition in a Mouse Model of Alzheimer's Disease - IOS Press",
, 26 April 2016 (2016-04-26), XP093155020,
Retrieved from the Internet:
URL:https://content.iospress.com/articles/journal-of-alzheimers-disease/jad151046

Re Item V

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

1 Claims 17,18,20,21 relate to a subject-matter considered by this Authority to be covered by the provision 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 in a first or further medical treatment.

Patentability, in particular novelty and inventive step, of claims 17,18,20,21 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

2 D2 discloses NTN1 neutralizing agents, e.g. an antibody, which bind to a netrin-1 receptor, e.g. UNC5C for treating cancer (the whole document, e.g. page 7, paragraphs 1-2; claims 1-11).

Thus, the subject-matter of claims 1,37,38,41 is not novel (Article 33(2) PCT).

3 D3 discloses polyclonal anti-UNC5C antibodies which -unless evidence to the contrary is provided - are expected to mimic/compete with netrin-1 binding to UNC5C. In the absence of any indication to the contrary, it is to be assumed that a prior-art antibody -here polyclonal anti-UNC5C antibodies - binding the same target antigen will have the claimed functional properties. Therefore a novelty objection is raised and the burden of proof lies with the applicant (the whole document, e.g. page 2, left-hand column, last paragraph, last half till right-hand column, paragraph 1). Thus, the subject-matter of claims 1,37,38,41 is not novel (Article 33(2) PCT).

4 D1 discloses that interfering with the ability of netrin-1 to inhibit DCC or UNC5H-induced cell death is associated with apoptosis of netrin-1-expressing tumor cells in vitro, and with inhibition of tumor growth or metastasis in different animal tumor (the whole document, e.g. abstract). D1 is silent about anti-UNC5C antibodies that mimic/compete with netrin-1 binding to UNC5C.

D5 discloses netrin-1 and netrin mimetics to treat AD (the whole document). D5 is silent about anti-UNC5C antibodies that mimic/compete with netrin-1 binding to UNC5C.

5 D3 discloses that blockade of secretase cleavage of UNC5C diminishes T835M mutant's proapoptotic activity, and that deletion of UNC5C from netrin-1–depleted mice attenuates AD pathologies and rescues cognitive disorders, and that AEP cleaves UNC5C, and thus may be beneficial for treating this AD, that deletion of UNC5C from netrin-1-depleted mice attenuates AD pathologies and rescues cognitive disorders, and D3 also discloses anti-UNC5C antibodies for

detecting UNC5C (the whole document, e.g. abstract; page 11, right-hand column, paragraph 1, third last sentence; page 2, left-hand column, last paragraph, last half till right-hand column, paragraph 1).

D4 discloses that blocking the aberrant apoptotic signaling of the T835M UNC5C variant may treat AD (the whole document, e.g. page 44, lines 9-11).

The document D3 or D4 is regarded as being the closest prior art to the subject-matter of the claim 42.

The subject-matter of claim 42 therefore differs from document D3 or D4 in that anti-UNC5C antibodies (that -as merely optional feature- mimic/compete with netrin-1 binding to UNC5C) are used.

The problem to be solved by the present invention may therefore be regarded as providing further means to treat a neurodegenerative disease or disorder.

The solution to this problem proposed by the present application consists of the provision of anti-UNC5C antibodies that mimic/compete with netrin-1 binding to UNC5C.

D2 discloses NTN1 neutralizing agents, e.g. an antibody, which bind to a netrin-1 receptor, e.g. UNC5C for treating cancer (the whole document, e.g. page 7, paragraphs 1-2; claims 1-11).

D3 and D4 already disclose that blocking or deleting UNC5C allows to treat AD. D3 and D4 would give the skilled person an incentive to target UNC5C for treating AD, e.g. by using UNC5C neutralizing antibodies as disclosed in D2.

Thus, the subject-matter of claims 1-42 is not inventive (Article 33(3) PCT).

6 The subject-matter of claims 1-42 is susceptible of industrial application (Article 33(4) PCT).

Re Item VIII

Certain observations on the international application

7 Art. 5 and/or 6 PCT:

- claim 1: the definition "the antibody mimics and/or competes with Netrin-1 for binding to UNC5C" is not clear
  - a) it is not clear what is meant with 'mimics',

- b) it would be an undue burden for the skilled person to randomly screen for antibodies which compete for Netrin-1 binding to UNC5C, which embraces also antibodies which block binding by sterical hindarance, and thus may not even bind within the similar region on UNC5C;

- claim 2-4,6-10: without any structural guidance it would be an undue burden for the skilled person to randomly screen for antibodies with the claimed properties; thus, e.g. the 6 CDRs of the antibody should be given; similar objections apply to claims 2,4,6-10;
- claim 5: it should be clarified what is meant with "UNC5C **in accordance with** SEQ ID NO: 99", does it mean that the antibody binds to SEQ ID NO: 99?
- claim 10: the specific region where the antibody binds should be given;
- claim 12, 13,16,17,19,21-28,31-34,37,41: it is essential to define an antibody by all six of its CDRs; even single mutations in the CDR regions can abolish antigen binding, thus, the exact sequence should be given, and the optional mutations should be deleted;
- claim 22, 32: several SEQ ID NO have no sequence, e.g. SEQ ID NO: 34, 177;
- claim 28-30,33: different methods to determine the CDRs exist, since the claim does not specify which one is used, the scope of the claim is unclear; same applies to framework regions;
- claim 35: it is not clear whether the antibody is e.g. a nanobody, or whether the antibody of the preceding claims comprises in addition to 6CDRs and framework regions, also a, e.g. nanobody;
- claim 35: it is not plausible that the 6 CDRs-antibody can be used as nanobody;
- claim 36: for the "IgG1 variant L234A/L235A" the species of origin should be given;
- claim 42: there are no clear properties or strucutral features given for the antibody used for therapy, it is not plausible that any anti-UNC5C can be used, be it for example agonistic or antagonistic, it would be an undue burden for the skilled person to randomly screen for antibodies with the claimed therapeutic effect; it is also noted that the reference to claim 1 in claim 42 is merely optional.

8 The expression "incorporated by reference" and similar expressions used throughout the description should have been deleted from the description. If matter in the documents referred to is essential to satisfy the requirements of Art. 5 PCT, then this matter should be expressly incorporated into the description.

9 The vague and imprecise statement "equivalents", "spirit of invention" and similar statements used throughout the description implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity of the claims (Art. 6 PCT) when used to interpret them. This statement should therefore have been amended to remove this inconsistency.