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/US2021/018989	22.02.2021	28.02.2020

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61K39/395 A61P37/00 A61P37/06

Applicant
ELI LILLY AND COMPANY

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:

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Date of completion of this opinion

see form PCT/ISA/210

Authorized Officer

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2021/018989

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:

      ☒ 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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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 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	1-36
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36
Industrial applicability (IA)	Yes:	Claims	1-36
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty (Art. 33(2) PCT), inventive step (Art. 33(3) PCT) or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1 PILAR BRITO-ZER?N ET AL: "IgG4-related disease: Advances in the diagnosis and treatment",
BAILLIERE'S BEST PRACTICE AND RESEARCH. CLINICAL REUMATOLOGY,
vol. 30, no. 2, 1 April 2016 (2016-04-01), pages 261-278, XP55395374, GB
ISSN: 1521-6942, DOI: 10.1016/j.berh.2016.07.003

D2 JONATHAN ZALEVSKY ET AL: "The impact of Fc engineering on an anti-CD19 antibody: increased Fc gamma receptor affinity enhances B-cell clearing in nonhuman primates",
BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US,
vol. 113, no. 16, 16 April 2009 (2009-04-16), pages 3735-3743, XP002685051,
ISSN: 0006-4971, DOI: 10.1182/BLOOD-2008-10-182048
[retrieved on 2008-12-24]

D3 Lawrence: "XmAb 5574, An Fc Engineered Humanized Anti-CD19 Monoclonal Antibody, Has Potent in Vitro and in Vivo Activities, and Has the Potential for Treating B Cell Malignancies | Blood | American Society of Hematology",
, 1 January 2008 (2008-01-01), XP55805140,
Retrieved from the Internet:
URL:https://ashpublications.org/blood/article/112/11/2621/60810/XmAbR5574-An-Fc-Engineered-Humanized-Anti-CD19
[retrieved on 2021-05-18]

D4 Su S ET AL: "Review Article Anti-CD19 Monoclonal Antibodies: a New Approach to Lymphoma Therapy",
IJMCM,
vol. 4, no. 3 1 January 2015 (2015-01-01), pages 143-151, XP55805142,
Retrieved from the Internet:

URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4644525/pdf/ijmcm-4-143.pdf
[retrieved on 2021-05-18]

The independent claims on file include the following:

1. An antibody that binds human CD19, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein
the HCDR1 comprises SEQ ID NO: 29,
the HCDR2 comprises SEQ ID NO: 30,
the HCDR3 comprises SEQ ID NO: 31,
the LCDR1 comprises SEQ ID NO: 32,
the LCDR2 comprises SEQ ID NO: 33, and
the LCDR3 comprises SEQ ID NO: 34.

(Pages 39, 40, Antibody CB3f/CB3)

5. An antibody that binds human CD19, wherein the antibody comprises a VH and a VL, wherein the VH comprises HCDR1, HCDR2, and HCDR3, and the VL comprises LCDR1, LCDR2, and LCDR3, wherein
the HCDR1 comprises SEQ ID NO: 29,
the HCDR2 comprises SEQ ID NO: 30,
the HCDR3 comprises SEQ ID NO: 31,
the LCDR1 comprises SEQ ID NO: 43,
the LCDR2 comprises SEQ ID NO: 44, and
the LCDR3 comprises SEQ ID NO: 45.

9. An antibody that binds human CD 19, wherein the antibody comprises a VH and a VL, wherein the VH comprises HCDR1, HCDR2, and HCDR3, and the VL comprises LCDR1, LCDR2, and LCDR3, wherein
the HCDR1 comprises SEQ ID NO: 15,
the HCDR2 comprises SEQ ID NO: 16,

the HCDR3 comprises SEQ ID NO: 17,
the LCDR1 comprises SEQ ID NO: 18,
the LCDR2 comprises SEQ ID NO: 19, and
the LCDR3 comprises SEQ ID NO: 20.

(Pages 36, 37, Antibody C323.C1)

14. A nucleic acid comprising a sequence encoding SEQ ID NO: 35, 52, 39, 46, 21, 54, or 25.

The proteins with the sequences set out in SEQ ID NO: 35, 52, 39, 46, 21, 54, or 25 are as follows:

SEQ ID NO:	Protein	
35	IgG4-S228P heavy chain, antibody **CB3f/CB3** (page 40)	
52	IgG1 Heavy chain, effector null, antibody **CB3f/CB3** (page 44)	
39	Light chain, antibody **CB3f** (page 41)	
46	Light chain, antibody **CB3** (page 42)	
21	IgG4-S228P heavy chain, antibody **C323.C1** (page 37)	
54	IgG1 Heavy chain, effector null, antibody **C323.C1** (page 46)	
25	Light chain, antibody **C323.C1** (page 38)	

This application concerns antibodies against human CD19. According to page 2 of the application, there is a need for anti-human CD19 antibodies that bind and inhibit human B cells without depleting them. Numerous antibodies binding human CD19 are known in the art (D4). D1-D3 each disclose anti-CD19 antibodies which are non-B cell depleting (see passages of these documents as indicated on the ISR).

In the work of the application, an antibody designated C323 against human CD19 was generated from a phage display library following panning of HEK cells transfected with CD19 and its coreceptor CD21. Affinity maturation and reversion to germline identity for certain residues in the 6 CDR sequences was carried out, generating an antibody designated CB3f with high affinity, low hydrophibicity, and low immunogenicity due to degree of germline identity (page 18, 2nd full paragraph).

Various isotype versions produced (IgG4 and IgG1) of CB3f were produced. CB3f was found to have good binding affinity for human and cynomolgous CD19. The antibody showed in vitro inhibition of B cell proliferation and activation, lack of in vitro CDC and ADCC, and a lack of induction of apoptosis. In vivo effects were shown including a reduction of clinical score in a collagen-induced arthrits model and an EAE model, and a delay of incdence in a type I diabetes model.

Although certain technical effects have been shown as associated with antibody CB3f, it is not clear that any claims on file properly include all technical features required for attaining any such effects (which due to target afffinity being one such effect likely include both CDR sequences (all 6) and FW regions). For binding antigen in the present instance, at least all 6 CDR sequences of any claimed antibody are deemed required, matter to which for instance claim 14 is not limited. Any technical effect related to a lack of B cell depletion is likely to be associated with a particular antibody Fc region (and as associated with a lack of CDC and ADCC, as shown in the application in the worked examples).

Over any of D1-D3 taken as closest prior art, the claims differ at least by the combination of the H chain or L chain CDR sequences. Given that no technical effect is able to be associated with this difference, the problem addressed is defined as how to

provide further antibodies to human CD19. Given that the provision of further antibodies binding a known target is routine in the art, the subject matter of the claims on file lacks inventive step.

Other comments

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. These comments may be applicable to present claims 27-29.