

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/US2019/050511	International filing date (day/month/year) 11.09.2019	Priority date (day/month/year) 14.09.2018
International Patent Classification (IPC) or both national classification and IPC INV. A61P37/06 A61P37/08 C07K16/28 A61K39/395 A61K39/00		
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 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 D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Hermann, Patrice Telephone No. +49 89 2399-0
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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:
 - ☒ 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:

see separate sheet

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	<u>1-41</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-41</u>
Industrial applicability (IA)	Yes: Claims	<u>1-41</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the report

Sequences SEQ ID NOs 1-17 from the sequence listing are also included in the basis of this written opinion.

Re Item V

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

1 Reference is made to the following documents:

- D1 US 2008/267967 A1 (GORCZYNSKI REGINALD M [CA] ET AL) 30 October 2008 (2008-10-30)
- D2 WO 2008/079352 A2 (SCHERING CORP [US]; PRESTA LEONARD G [US] ET AL.) 3 July 2008 (2008-07-03)
- D3 David A Copland ET AL: "Immunopathology and Infectious Disease Monoclonal Antibody-Mediated CD200 Receptor Signaling Suppresses Macrophage Activation and Tissue Damage in Experimental Autoimmune Uveoretinitis", The American Journal of Pathology, vol. 171, No. 2, 1 January 2007 (2007-01-01), pages 580-588070272, XP055413886
- D4 Y. LIU ET AL: "CD200R1 Agonist Attenuates Mechanisms of Chronic Disease in a Murine Model of Multiple Sclerosis", THE JOURNAL OF NEUROSCIENCE, vol. 30, no. 6, 10 February 2010 (2010-02-10), pages 2025-2038, XP055413887
- D5 WO 03/077947 A1 (SCHERING CORP [US]) 25 September 2003 (2003-09-25)
- D6 MUNIR AKKAYA ET AL: "Dissection of Agonistic and Blocking Effects of CD200 Receptor Antibodies", PLOS ONE, vol. 8, no. 5, 14 May 2013 (2013-05-14), page e63325, XP055647634

- D7 CHERWINSKI H M ET AL: "The CD200 receptor is a novel and potent regulator of murine and human mast cell function", THE JOURNAL OF IMMUNOLOGY, THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS, INC, US, vol. 174, no. 3, 1 February 2005 (2005-02-01), pages 1348-1356, XP002495063
- D8 MIRIAM HERNANGÓMEZ ET AL: "CD200R1 agonist attenuates glial activation, inflammatory reactions, and hypersensitivity immediately after its intrathecal application in a rat neuropathic pain model", JOURNAL OF NEUROINFLAMMATION, vol. 13, no. 1, 18 February 2016 (2016-02-18), XP055647631
- 2 None of the prior-art at hand discloses the subject-matters of present claims 1-41. Claims 1-41 appear therefore to meet the requirements of Article 33(2) PCT.
- 3 However, the subject-matters of claims 1-41 do not appear to be based on an inventive concept and claims 1-41 therefore lack an inventive step required to fulfill Articles 33(1) and (3) PCT, the reasons being as follows:
- 3.1 Document D1 already discloses agonist anti-CD200R monoclonal antibodies and the use thereof in the in vivo mice models of collagen-induced arthritis, skin allotransplantation, induced tolerance to kidney transplant (cf. D1 abstract, [0009] - [[0029], [0161] - [0169], examples 1-8 and claims).
- 3.2 Document D1 is considered to represent the closest prior-art for the subject-matter of independent claim 1 which differs therefrom in that the antibody of independent claim 1 is an anti-CD200R antibody comprising distinct amino acid sequences characterising its 6 complementary determining regions (CDRs) distributed on each of its heavy- and light-chains.
- 3.3 The application as originally filed fails however to demonstrate that said specific monoclonal antibody characterised by said specific features, i.e. the specific amino acid sequences of its CDRs, in comparison to the anti-CD200R monoclonal antibodies already disclosed in the art, e.g. in document D1, lead to an unexpected technical effect or represent a solution to a particular and yet to be identified objective technical problem in the art.
- 3.4 Hence in view of document D1 selected as closest state of the art, the objective technical problem to be solved can only be seen as the provision of an alternative agonist anti-CD200R monoclonal antibody.

- 3.5 The solutions proposed in independent claim 1, i.e. the specific anti-CD200R monoclonal antibody, is not considered inventive because the generation of further alternative monoclonal antibodies is a matter of the skilled person's routine experimentation and the choice of said particular monoclonal antibody is arbitrary since, in the absence of evidence to the contrary, said choice is not associated with any particular technical effect other than the well known possibility to use it in prevention and/or therapy. Hence the subject-matter of claim 1 is not considered inventive and claim 1 would not be considered to meet the requirements of Articles 33(1) and 33(3) PCT.
- 3.6 An identical objection applies *mutatis mutandis* to the subject-matter of independent claim 29, since, in the absence of evidence to the contrary, it is presently considered that the anti-CD200R monoclonal antibody disclosed in the prior art document D1 does not cause significant cytokine release compared to a wild-type IgG1 antibody having the same CDRs as said anti-CD200R agonist antibody.
- 3.7 In view of the prior-art documents at hand, dependent claims 2-28 and 29-31 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 (Articles 33(1) and 33(3) PCT) since these additional features appear to be conventional and do not appear to result in any unexpected effect (Articles 33(1) and 33(3) PCT).
- 3.8 Given that an inventive step for the antibodies of claims 1-28 would not be acknowledged, it is considered that the provision of nucleic acids encoding said non inventive anti-CD200R antibody (claims 37-40) and host cells transformed with said nucleic acid (claim 41), pharmaceutical composition comprising said non-inventive antibody (claim 36) and uses thereof either for the treatment of inflammatory diseases, allergy, asthma, and/or further autoimmune diseases (claims 32-35) represent all routine experimentation the skilled person would perform without the need of inventive skills contrary to the requirements of Article 33(1) and 33(3) PCT.
- 4 Similarly a lack of inventive step could also be raised when departing from any of the documents D2 or D3 taken into consideration separately as representing the closest state of the art. For instance, each of these documents discloses agonist anti-CD200R monoclonal antibodies and their potential use therapy for the treatment of autoimmune disorders or further inflammatory diseases (cf. D2 abstract, [0007] - [0022], [0091] - [0124], examples 1-11 and claims ;D3

abstract, p. 581 left-hand column third full paragraph, p. 584 left-hand column second full paragraph - p. 586 left-hand column line 13, p. 587 left-hand column line 12 - p. 588 left-hand column line 9, figures 3-7).

- 5 The applicant's attention is drawn to the fact that it is well accepted in the art of antibodies that amino acid sequences of the CDRs of the light- and the heavy-chain variable regions, in the appropriate order, are considered as necessary to define the target specificity of a claimed antibody. However if an inventive activity of a claim to an antibody lays on a particular technical or surprising effect of said antibody due to its particular and very specific affinity, avidity, or biological effect upon binding to its target epitope, e.g. agonist/activating effect (for example implicating effects linked to Fc region, as it is presently the case (cf. examples of the instant application)), the claim wording should then define the amino acid sequences of the CDRs completed by the frameworks amino acid sequences, both in the appropriate order on the heavy- and light-chain variable regions of the claimed antibody (and eventually the structural characteristic features of the Fc region responsible for the biological activity). Indeed, the particular properties cited herein above are known to be entirely linked not only to the epitope recognition, but also to its interaction with the CDRs in a very specific paratope conformation that depends entirely on the frameworks amino acid sequences of said antibody. For instance, in line of this remark, it is considered that instant claims 1-41 do not comprise all the essential characteristic structural features that would appear to be compulsory for the exact definition of the product claimed, i.e. a product that might be seen as presenting a particular or surprising technical effect in the art and on which the applicant would like an inventive step to be assessed. Claims 1-41 are therefore considered to lack clarity contrary to the requirements of Article 6 PCT, and a person skilled in the art wishing to repeat the claimed subject-matter and arrive at a potential but yet unforeseeable objective technical effect in the art, would be thus facing undue burden/experimentation contrary to the requirements of Article 5 PCT.
- 6 claims 20 and 22 lack clarity since their respective subject-matter contains further features that do not represent features of the antibody *per se* to which the claims, on which they respectively depend, relates (Article 6 PCT).
- 7 The expression "*significant cytokine release*" is a relative expression and leaves the reader in doubt as to the exact claim scopes. Hence claims 5 and 29 lack clarity (Article 6 PCT).

- 8 Claims comprising the term "*agonist*", that represents a desiderata, without however defining the exact and essential structural characteristic features of the product to be indeed regarded as an "agonist", lack clarity, essential features contrary to the requirements of Article 6 PCT. Said claims are also considered insufficiently disclosed in the application as filed contrary to the requirements of Article 5 PCT, since the person skilled in the art would be facing undue burden/experimentation when trying to repeat their respective subject-matter. This is presently the case for claims 6.
- 9 It is highly doubtful that all of the products covered by the broad scopes of claims 1-31 would lead to the expected effect contained in presently on file claims 32-35. Hence, claims 32-35 are considered to be insufficiently disclosed in the application as originally filed contrary to the requirements of Article 5 PCT. It appears that claims 32-35, furthermore, do not meet the requirements of Article 6 PCT for lack of essential characteristic features of the product to which they relates, features that are considered compulsory in order to arrive at the expected effect, i.e. the respective treatment recited in claims 32-35.
- 10 Claim 29 is considered to lack clarity contrary to the requirements of Article 6 PCT due to the presence of the expression "*wherein the antibody does not cause significant cytokine release compared to a wild-type IgG1 antibody having the same CDRs as the CD200R agonist antibody*". Indeed said expression corresponds to a result-to-be-achieved, however the claim is silent as regards the structural characteristic features the antibody should present in order to arrive at said result. The person skilled in the art would therefore be facing undue experimentation/burden when trying to repeat the claimed subject-matter. Hence claim 29 is also insufficiently disclosed in the application as originally filed contrary to the requirements of Article 5 PCT.
- 11 As regards claims 32-35 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 32-43 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.