

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

see form PCT/ISA/220

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
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International application No. PCT/US2015/030275	International filing date (day/month/year) 12.05.2015	Priority date (day/month/year) 19.05.2014
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International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 C07K16/22 C07K16/46 A61K39/395 A61P35/00

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Covone-van Hees, M Telephone No. +31 70 340-0
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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:

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>1-31</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>3-14, 16-31</u>
	No: Claims	<u>1, 2, 15</u>
Industrial applicability (IA)	Yes: Claims	<u>1-31</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

1 **Re Item V**

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

1.1 Claims 25-27 relate to subject-matter considered by this Authority to be covered by the provisions 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 use in a first or further medical treatment.

1.2 **Novelty** (Art.33(2) PCT)

1.3 Claim 1 refers to a compound comprising an antibody fused by linkers to two scFv defined by sequences. The binding regions of the antibodies bind to VEGFR2 and Ang-2. The order of the different components in the compound is however not specified.

1.4 In the prior art it is known that inhibition of both pathways i.e. VEGF and Ang-2 improves the outcome of cancer. Daly et al. (D1) suggests that the dual inhibition of VEGF and Ang-2 pathways may enhance the clinical benefit of anti-VEGF agents alone (whole doc). This suggestion is confirmed in several documents: Doppalapudi et al. (D2) show that the bispecific anti-Ang-2 and anti-VEGF Ab is much more effective in tumour treatment than the single antibodies (pg.22613 col.2 para.2 - pg.22615 col.1; fig.4). In their study, Jendreyko et al. (D3), WO2010040508 (D4) and WO2011/117329 (D5) concludes that simultaneous inhibition of VEGF and Tie-2 pathways, using a bispecific anti-VEGF/anti-Ang-2 Ab, has additive antiangiogenic effect (D3:fig. 2; Results; D4 and D5 examples). EP2433868 (D6) produces an anti-VEGFR2 Ab, fused at its light chain to an Ang2 binding domain binding to Tie-2, called dual targeting antibody, (para45,52) and tests the inhibition of blood vessels formation and tumour growth (ex.5-8).

1.5 None of the available prior art documents discloses the compound referred to in claim 1, the subject-matter of claim 1 is therefore novel.

1.6 Remaining claims are all dependent on claim 1, refer back to it or comprise the same distinguishing features of claim 1 and as such are also novel (Art.54 EPC).

2 **Inventive Step** (Art.33(3) PCT)

2.1 In the description pg.2 l.13-23 the Applicant explained that in order to produce the specific compounds they had to overcome technical difficulties, due to

- light chain mis-pairing. The specific construct ie. claims 3-14,16-20 and claims referring back to them are not obvious over the available prior art.
- 2.2 Claims comprising the distinguishing features of said claims are accordingly also inventive.
- 2.3 Claims 1,2,15 are not inventive over the available prior art, since the production of alternative bispecific Ab is obvious over at least D4 and D5, disclosing alternative bispecific Ab, binding to different targets, but inhibiting the same pathways. Additionally, these claims lack essential features leading to the inventive effect ie. the order of the compounds (as in claim 2) and the specific pairing of heavy and light chains.

3 Re Item VII

Certain defects in the international application

- 3.1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in WO2010040508 (D4) and WO2011/117329 (D5) is not mentioned in the description, nor are these documents identified therein.

4 Re Item VIII

Certain observations on the international application

- 4.1 It is clear from the description on pages 2 I.13-23 that the order and specific pairing of heavy and light chain are essential to the definition of the invention. Since independent claims 1,2,15 do not contain these features they do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.
- 4.2 For the sake of clarity, the Applicant is kindly requested to specify the binding specificity of the antibodies at least in the independent product claims.

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