

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/US2020/039477

International filing date (day/month/year)
25.06.2020

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27.06.2019

International Patent Classification (IPC) or both national classification and IPC
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Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

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:



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Date of completion of
this opinion

see form
PCT/ISA/210

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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. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-17(partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for the whole application or for said claims Nos. 1-17(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-17(partially)

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 | |
| | No: Claims | <u>1-17(partially)</u> |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | <u>1-17(partially)</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-17(partially)</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

Re Item IV

Lack of unity of invention

The following inventions were identified in the application:

1. claims: 1-17(partially)

An anti-ANGPT2 antibody or an antigen-binding fragment comprising: a heavy chain variable region comprising the amino acid sequence of SEQ ID NO. 13 (H-CDR1); the amino acid sequence of SEQ ID NO. 15 (H-CDR2); and the amino acid sequence of SEQ ID NO. 17 (H-CDR3), and a light chain variable region comprising the amino acid sequence of SEQ ID NO. 19 (L-CDR1); the amino acid sequence of SEQ ID NO. 22 (L-CDR2); and the amino acid sequence of SEQ ID NO. 24 (L-CDR3).
2. claims: 1-17(partially)

An anti-ANGPT2 antibody or an antigen-binding fragment comprising: a heavy chain variable region comprising the amino acid sequence of SEQ ID NO. 14 (H-CDR1); the amino acid sequence of SEQ ID NO. 15 (H-CDR2); and the amino acid sequence of SEQ ID NO. 17 (H-CDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO. 19 (L-CDR1); the amino acid sequence of SEQ ID NO. 22 (L-CDR2); and the amino acid sequence of SEQ ID NO. 24 (L-CDR3),
3. claims: 1-17(partially)

An anti-ANGPT2 antibody or an antigen-binding fragment comprising: a heavy chain variable region comprising the amino acid sequence of SEQ ID NO. 13 (H-CDR1); the amino acid sequence of SEQ ID NO. 15 (H-CDR2); and the amino acid sequence of SEQ ID NO. 16 (H-CDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO. 20 (L-CDR1); the amino acid sequence of SEQ ID NO. 23 (L-CDR2); and the amino acid sequence of SEQ ID NO. 24 (L-CDR3),
4. claims: 1-17(partially)

An anti-ANGPT2 antibody or an antigen-binding fragment comprising: a heavy chain variable region comprising the amino acid sequence of SEQ ID NO. 13 (H-CDR1); the amino acid sequence of SEQ ID NO. 15 (H-CDR2);

and the amino acid sequence of SEQ ID NO. 16 (H-CDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO. 21 (L-CDR1); the amino acid sequence of SEQ ID NO. 23 (L-CDR2); and the amino acid sequence of SEQ ID NO. 25 (L-CDR3),

5. claims: 1-17(partially)

An anti-ANGPT2 antibody or an antigen-binding fragment comprising: a heavy chain variable region comprising the amino acid sequence of SEQ ID NO. 13 (H-CDR1); the amino acid sequence of SEQ ID NO. 15 (H-CDR2); and the amino acid sequence of SEQ ID NO. 16 (H-CDR3); and a light chain variable region comprising the amino acid sequence of SEQ ID NO. 20 (L-CDR1); the amino acid sequence of SEQ ID NO. 22 (L-CDR2); and the amino acid sequence of SEQ ID NO. 24 (L-CDR3).

The above identified inventions could only fulfil the unity requirements of the PCT (Rule 13) in the event that they were linked by a special technical feature as to form a single general inventive concept according to Rule 13.2 PCT, i.e., that there was a technical relationship among them involving one or more of the same or corresponding special technical features in the sense of Rule 13.1 PCT. If a group of inventions is claimed, the requirement that the inventions in this group are so linked as to form a single general concept is fulfilled only if there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features, i. e. special common matter. The term "special" means that the features in question define the contribution that the invention considered as a whole makes over the prior art in terms of novelty and inventive step. The term "same" means that the special technical features are identical or define an identical chemical structure. The term "corresponding" means that the special technical features achieve the same technical effect or solve the same technical problem.

In particular, in the case of features defining technical alternatives, if the common technical effect to be achieved is already known, or may be recognised as generally desirable (a mere desideratum), or is obvious, these alternative features are not considered as defining a technical relationship because there is no inventive merit in formulating the problem.

If common matter is identified and, in the light of the prior art at hand, comprises any same or corresponding technical features that appear to contribute to the achievement of at least one new technical effect in a non-obvious way, then these features define a technical relationship between the remaining claims, and the requirements of unity of invention are fulfilled.

The common matter linking the alternatives within independent claim 1 is the following:

Anti-ANGPT2 antibodies.

This common matter does not comprise a single general inventive concept in the sense of 13.2 PCT, based on the same or corresponding special technical features, because anti- ANGPT2 for the therapy of solid tumors are disclosed in D1 (abstract) to D4 (respective passages see below) . The remaining features are the amino acid sequences of the CDRs of the antibodies, which are structurally distinct. In the absence of same or corresponding special technical features and as the other features are structurally unrelated, there is lack of unity and each anti-ANGPT2 antibody defines an independent invention.

The technical features, representing the difference over the non-inventive common matter are the structurally different antibodies. Each of the antibodies solves the problem of providing an alternative antibody specific for ANGPT2. Hence, the above defined separate inventions or groups of inventions are not so linked as to form a single general inventive concept.

Only the first invention was searched. Thus this report is limited to the first invention.

Re Item V

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

Reference is made to the following documents:

- D1 KYRIAKOS P. PAPADOPOULOS ET AL: "A Phase I First-in-Human Study of Nesvacumab (REGN910), a Fully Human Anti-Angiopoietin-2 (Ang2) Monoclonal Antibody, in Patients with Advanced Solid Tumors", CLINICAL CANCER RESEARCH, vol. 22, no. 6, (2015-10-21), pages 1348-1355, XP55728926
- D2 EP 2 832 746 A1 (SAMSUNG ELECTRONICS CO LTD [KR]) (2015-02-04)

D3 WO 2015/091655 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) (2015-06-25)

D4 WO 2013/134516 A1 (MEDIMMUNE LLC [US]; ALITALO KARI [FI] ET AL.) (2013-09-12)

The document D1 discloses (abstract: fully human monoclonal anti-Angiopoietin-2 antibody Nesvacumab (REGN910) inactivates Ang2 (Tie2 receptor ligand) with high affinity and shows no binding to Ang1. Clinical trial an patients with advanced solid tumors.

The document D2 discloses (claims 1-8) anti-Ang2 antibody specifically binds to an angiogenesis-inducing factor Angiopoietin-2 (Ang2) and complexes with a Tie2 receptor while bound to Ang2

The document D3 discloses (claims 1-15) a combination therapy with an anti-ANG2 antibody and a CD40 agonist.

the document D4 discloses (example 12) a clinically feasible method of allograft protection with an intracoronarily administered single dose of endogenous Ang2 neutralizing anti-Ang2 antibody. Anti-Ang2 antibody therapy inhibited the IRI-induced microvascular dysfunction and subsequent development of cardiac fibrosis and chronic allograft vasculopathy. Single dose treatment with anti-Ang2 inhibited IRI-associated early innate immune activation.

The cited documents do not disclose the combination of the CDR sequences SEQ ID NO: 13, 15, 17, 19, 22, 24. Thus the subject-matter of claims 1-17 is formally novel.

The document D1 could be considered the closest prior art. The difference to the subject matter of claim 1 is the sequence of the CDR regions of the heavy and light chains. No unexpected effect related to this difference has been shown in the application. Thus the problem to be solved is considered the provision of an alternative anti-ANGPT2 antibody.

The provision of an antibody specific to a known target is considered common practise in the field. The amino acid sequence of the CDRs of the heavy and light chains of the antibody is considered an arbitrary selection, that does not involve an inventive step.

The same argumentation applies mutatis mutandis to the subject-matter of claims 1-8, 14-17.

The features of the dependent claims 2-3, 9-13 do not appear to overcome the lack of inventive step as no unexpected effect appears to be related to those features and are either considered arbitrarily selected or routine practise in the field.

Thus the subject-matter of claims 1-17 does not involve an inventive step in the sense of Article 33(3) PCT, and the criteria of Article 33(1) PCT are therefore not met.

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 5-16 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Re Item VIII

Certain observations on the international application

The subject-matter of claim 1 is not clear (Article 6 PCT) as terms put into brackets introduce ambiguity and are considered optional . For an antibody the correct order of the CDRs and their position in the framework regions is considered an essential features, that is missing from claim 1.

Terms put into brackets like "(and associated disorders)" are considered optional features and induce ambiguity on the scope of the claim. Moreover, the term "associated disorders² is vague. The requirements of Article 6 PCT are thus not met.

The application does not show data indicating a special effect on treatment of the diseases listed in claims 9, 10, 11, which leads to issues under Article 5 PCT.