

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

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Date of mailing
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Applicant's or agent's file reference
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FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 22/11669

International filing date (day/month/year)

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08 January 2021 (08.01.2021)

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CPC - A61P 7/02, C07K 16/36, C07K 16/4028, A61K 31/4162, A61K 31/506

Applicant **BRISTOL-MYERS SQUIBB 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 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/US
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Date of completion of this opinion

08 May 2022

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Box No. I Basis of this 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(b)).
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:

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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. 7-13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35-57

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. see below are so unclear that no meaningful opinion could be formed (*specify*):

Claims 7-13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35-57 are held unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).

- ☐ 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 said claims Nos. 7-13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35-5

- ☐ 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 13*ter*. I(a) or (b).

- ☐ See Supplemental Box for further details.

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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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Groups I+: Claims 1-6, drawn to an isolated antigen binding peptide. The composition will be searched to the extent that the antibody encompassing VH-CDR1 and VL-CDR1 of SEQ ID NOs: 1 and 29, respectively, VH and VL of SEQ ID NOs: 52 and 84, respectively. It is believed that claims 1-2, (5-6)(in part) encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass SEQ ID NOs: 1, 29, 52 and 84. Additional antigen binding peptide(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected antigen binding peptide(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be an antigen binding peptide encompassing VH-CDR1-3 and VL-CDR-1-3 of SEQ ID NOs: 1, 14, 23, 29, 38 and 45, respectively; VH and VL of SEQ ID NOs: 53 and 85, respectively (Claims 1-6).

Groups II+: Claims 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, drawn to an isolated antibody Fab fragment that specifically binds to the compound of Formula (II). Group II+ will be searched upon payment of additional fees. The composition may be searched, for example, to the extent that the Fab fragment encompasses SEQ ID NOs: 106 and 164, for an additional fee and election as such. It is believed that claim 14 read on this exemplary invention. Additional Fab fragment(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected Fab fragment(s). Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. Another exemplary election would be a Fab fragment encompassing SEQ ID NOs: 180 and 164 (Claim 16).

The inventions listed as Groups I+ and II+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

Groups I+ include the special technical feature of an isolated antigen binding peptide comprising specific amino acid sequences for VH-CDRs, VL-CDRs, VH and VL, not required by Groups II+.

Groups II+ include the special technical feature of an isolated antibody Fab fragment that binds to the compound of Formula (II), not required by Groups I+.

No technical features are shared between the amino acid sequences of Groups I+ and II+, accordingly, these groups lack unity a priori.

-----continued in Supplemental Box-----

4. Consequently, this opinion has been established in respect of the following parts of the international application:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-2, (5-6)(in part) limited to SEQ ID NOs: 1, 29, 52, 84

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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

1. Statement

Novelty (N)	Claims	1-2, (5-6)/(1-2)	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1-2, (5-6)/(1-2)	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1-2, (5-6)/(1-2)	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-2, (5-6)/(1-2) meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest to an isolated antigen binding peptide comprising VH-CDR1 SEQ ID NO: 1 and VL-CDR1 SEQ ID NO: 29 or an isolated antigen binding peptide comprising VH SEQ ID NO: 51 and VL SEQ ID NO: 84.

Regarding claim 1, US 2014/0186362 A1 to NovImmune S.A. (hereinafter "NovImmune") teaches an isolated antigen binding peptide comprising at least one heavy chain variable region (VH) and at least one light chain variable region (VL), wherein the at least one VH comprises at least one of:

(a) a VH complementarity-determining region 1 (VH-CDR1) comprising an amino acid sequence of SEQ ID NO: 1 (abstract, The invention relates to fully human antibodies, and fragments thereof, that bind to human interferon gamma (hIFNgamma), thereby modulating the interaction between IFNgamma and its receptor, IFNgamma-R, and/or modulating the biological activities of IFNgamma.; Fig. 6A VH PROTEIN SEQUENCE SEQ ID NO: 43.; Note, SEQ ID NO: 43 is 100% match to SEQ ID NO: 1 of instant claim.).

US 2008/0160035 A1 to Stevens et al. (hereinafter "Stevens") teaches an isolated antigen binding peptide comprising at least one heavy chain variable region (VH) and at least one light chain variable region (VL), wherein the at least one VL comprises at least one of:

(d) a VL-CDR1 comprising an amino acid sequence consisting of SEQ ID NO: 405 (Claim 1, An antibody or antigen-binding fragment thereof, that specifically binds hIL-4R (SEQ ID NO:1) with a KD of about 200 pM or less.; Claim 4, The antibody or antigen-binding fragment of claim 3, further comprising a light chain variable region (LCVR) selected from the group consisting of SEQ ID NO: 11.....405.; Note, SEQ ID NO: 405 (amino acid 24-34) is 90% match SEQ ID NO: 29 of instant claim.), but does not specifically teach SEQ ID NO: 29.

Regarding claim 2, US 2018/0134787 A1 to Eureka Therapeutics, Inc. (hereinafter "Eureka") teaches an isolated antigen binding peptide comprising:

(a) at least one heavy chain variable region comprising an amino acid sequence consisting of SEQ ID NO: 16 (abstract, Described herein are human antibody agents and multi-specific binding agents that specifically bind human CD 19, in particular, native human CD 19.; para [0061], a human antibody agent comprises a heavy chain variable region having a sequence that is at least 95% identical to the heavy chain variable region sequence that appears in SEQ ID NO:16.; Note, SEQ ID NO: 16 is 90% match SEQ ID NO: 52 of instant claim.), but does not specifically teach SEQ ID NO: 52.

Stevens teaches an isolated antigen binding peptide comprising:

(b) at least one light chain variable region comprising an amino acid sequence consisting of SEQ ID NO: 405 (Claim 1, An antibody or antigen-binding fragment thereof, that specifically binds hIL-4R (SEQ ID NO:1) with a KD of about 200 pM or less.; Claim 4, The antibody or antigen-binding fragment of claim 3, further comprising a light chain variable region (LCVR) selected from the group consisting of SEQ ID NO: 11.....405.; Note, SEQ ID NO: 405 is 97% match SEQ ID NO: 84 of instant claim.), but does not specifically teach SEQ ID NO: 84.

There is no prior art that teaches or fairly suggests to one of ordinary skill in the art, in view of the teachings of NovImmune and Stevens, to have prepared an isolated antigen binding peptide comprising VH-CDR1 SEQ ID NO: 1 and VL-CDR1 SEQ ID NO: 29.

There is no prior art that teaches or fairly suggests to one of ordinary skill in the art, in view of the teachings of Eureka and Stevens, to have prepared an isolated antigen binding peptide comprising VH SEQ ID NO: 52 and VL SEQ ID NO: 84.

Regarding claims (5-6)/(1-2), the claims are dependent on claims 1-2, and thus, meet the criteria set out in PCT Article 33(2)-(3), as discussed above.

Claims 1-2, (5-6)/(1-2) have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box No. IV(3) Lack of unity of invention

Common Technical Features

Additionally, even if Groups I+ and II+ were considered to share the technical features of including: an isolated antibody, these shared technical features are previously disclosed by WO 2020/216379 A1 to (I-MAB).

I-MAB teaches (instant claim 1) an isolated antigen binding peptide comprising at least one heavy chain variable region (VH) and at least one light chain variable region (VL), wherein the at least one VH comprises at least one of:

(a) a VH complementarity-determining region 1 (VH-CDR1) comprising an amino acid sequence consisting of SEQ ID NO: 1; and wherein the at least one VL comprises at least one of:

(e) a VL-CDR2 comprising an amino acid sequence consisting of SEQ ID NO: 38 (abstract, Provided are full human anti-PD-L1 antibodies or fragments thereof. In various examples, the antibodies or fragments thereof include a VH CDR1, a VH CDR2, a VH CDR3, a VL CDR1, a VL CDR2, and a VL CDR3 which are selected from sequence groups of SEQ ID NO: 35-42, SEQ ID NO: 43-51, SEQ ID NO: 52-66, SEQ ID NO: 67-79, SEQ ID NO: 80-88 and SEQ ID NO: 89-102, respectively, para [0006]. In an example antibody or fragment, VH comprises the amino acid sequence of SEQ ID NO: 23, 124, 126, 127, 128, 130, 140, or 145, and the VL comprises the amino acid sequence of SEQ ID NO: 24 or 125, as well as their variants.; para [0037], Table A CDR sequence from antibodies B01-B17 (Kabat); HCDR1 SEQ ID NO: 42 (SNAMS); LCDR2 SEQ ID NO: 80 (AASSLQS).; Note, SEQ ID NOs: 42 and 80 are 100% match to SEQ ID NO: 1 and 38 of instant claim.).

The inventions of Groups II+ share the technical feature of an isolated antibody Fab fragment that specifically binds to the compound of Formula (II).

However, these shared technical features do not represent a contribution over prior art in view of the abstract "FEIBA and Novoseven Neutralize the Anticoagulant Effects of a Novel Small Molecule FXIa Inhibitor BMS-986177/JNJ-70033093 in Human Plasma and Whole Blood in Vitro" by Bunce et al. (hereinafter "Bunce") (Blood, 05 November 2020, 136, Supplement 1: 10) and WO 2020/089380 A1 to Bayer Aktiengesellschaft (hereinafter "Bayer").

Bunce teaches (instant claim 14) an isolated compound that specifically neutralizes to the compound of Formula (II) (abstract, Background: FXIa inhibition is a promising antithrombotic drug target. BMS-986177/JNJ-70033093 (BMS-177/JNJ-3093) is a novel small molecular inhibitor of FXIa currently in Phase II clinical trials with the potential for reduced bleeding risk.; Note, BMS-986177 corresponds to Formula (II) of instant claim.; Aim: To evaluate the ability of nonspecific reversal agents (NSRAs) FEIBA, NovoSeven, Kcentra, Profilnine, BeneFix, Novoeight, and Cyklokapron to neutralize the anticoagulation of BMS-177/JNJ-3093 in the activated partial thromboplastin time (aPTT), thromboelastography (TEG) and thrombin generation assay (TGA) in vitro using human plasma or whole blood.; Results: FEIBA effectively neutralized the anticoagulant effects of JNJ-3093 in aPTT, TEG and TGA.).

Bunce does not specifically teach an isolated antibody Fab fragment that binds to the compound of Formula (II). Bayer teaches an isolated antibody Fab fragment that binds to inhibitor of FXIa (abstract, The present invention relates to reversal agents, which specifically bind to the anti-FXIa antibody 076D-M007-H04-CDRL3-N110D as described in WO2013/167669, and neutralize the therapeutic activity of this anti-FXIa antibody, as well as to compositions comprising these reversal agents. Methods of obtaining the antibodies or antigen-binding fragments thereof (such as Fab fragments) and nucleic acids encoding the same, are also provided.). It would have been obvious to one of ordinary skill in the art to have developed an isolated antibody Fab fragment as an reversal agent, as taught by the Bayer, to counteract the compound of Formula (II), as taught by Bunce.

As said technical features were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the groups.

Groups I+ and II+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Item 4 (continued):

Claims 7-13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35-57 are held unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).