

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

04 SEP 2018

Applicant's or agent's file reference
24453

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US2018/030516

International filing date (day/month/year)

01 May 2018

Priority date (day/month/year)

02 May 2017

International Patent Classification (IPC) or both national classification and IPC

IPC(8) - A61K 39/00; A61K 39/395; A61P 31/12; A61P 35/00 (2018.01)

CPC - A61K 39/39558; A61K 2039/507; C07K 16/2803; C07K 2317/14; C07K 2317/24 (2018.08)

Applicant MERCK SHARP & DOHME CORP.

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
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450
Facsimile No. 571-273-8300

Date of completion of this opinion

01 August 2018

Authorized officer

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2018/030516

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(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:

SEQ ID NOs: 100-115, 148, 152, 154, and 291-293 were searched.

**WRITTEN OPINION OF THE
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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. 5-30

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. 5-30 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 5-30 are multiple dependent claims 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. 5-30

☐ 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.

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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	1-4	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-4	NO
Industrial applicability (IA)	Claims	1-4	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-4 lack an inventive step under PCT Article 33(3) as being obvious over Williams et al. (hereinafter Williams) in view of Bristol-Myers Squibb Company and Adler et al. (hereinafter Adler).

Regarding Claim 1, Williams discloses a formulation (To prepare pharmaceutical or sterile compositions of the anti-TIGIT antibodies and antigen-binding fragments of the invention (e.g., 14A6, 28H5, 31C6 and humanized versions thereof), the antibody or antigen-binding fragment thereof is admixed with a pharmaceutically acceptable carrier or excipient, Para. [0336]; formulations, Para. [0337]) comprising: (i) about 5 mg/ml to about 200 mg/ml of an anti-TIGIT antibody, or antigen binding fragment thereof (Antibodies or antigen-binding fragments thereof disclosed herein (e.g., 14A6, 28H5, 31C6 and humanized versions thereof) may be provided ...dose ...5.0 mg/ml, Para. [0347]); (ii) about 5 mM to about 20 mM buffer (The formulation buffers were specific for each antibody to stabilize proteins and prevent precipitation ...10mM sodium phosphate, Para. [0399]); (iii) about 6% to about 8% weight / volume (w/v) non-reducing sugar (7% sucrose, Para. [0399]), but fails to explicitly disclose about 10 mg/ml to about 200 mg/ml of an anti-TIGIT antibody, or antigen binding fragment thereof (iv) about 0.01 % to about 0.10% (w/v) non-ionic surfactant; and (v) about 1 mM to about 20 mM anti-oxidant.

Bristol-Myers Squibb Company is in the field of antibodies to TIGIT (Abstract) and teaches about 10 mg/ml to about 200 mg/ml of an anti-TIGIT antibody, or antigen binding fragment thereof (a composition comprises an anti-TIGIT antibody at a concentration of at least ...10 mg/mL, Para. [0255]).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Williams with the teaching of Bristol-Myers Squibb Company for the purpose of achieving the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient (Bristol-Myers Squibb Company, Para. [0271]).

Modified Williams fails to explicitly disclose iv) about 0.01 % to about 0.10% (w/v) non-ionic surfactant; and (v) about 1 mM to about 20 mM anti-oxidant.

Adler is in the field of antibody formulations (Abstract) and teaches iv) about 0.01 % to about 0.10% (w/v) non-ionic surfactant (When polysorbate 20 (Tween 20™) and polysorbate 80 (Tween 80™) are used as surfactants they are generally used in a concentration range ...of about 0.01 % to about 0.1 % w/v (weight/volume), Para. [0052]); and (v) about 1 mM to about 20 mM anti-oxidant (a stabilizer selected from 10 mM methionine, Para. [0019]; A subgroup within the stabilizers are antioxidants, Para. [0047]).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Williams with the teaching of Adler for the purpose of allowing for intravenous administration (Adler, Para. [0128]).

Regarding Claim 2, modified Williams discloses the formulation of claim 1. Williams further discloses wherein the anti-TIGIT antibody or antigen binding fragment thereof comprises three light chains CDRs comprising CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, CDRL3 of SEQ ID NO: 113 (the invention provides an isolated antibody or antigen binding fragment thereof that binds to human TIGIT comprising a heavy

chain variable region comprising SEQ ID NO:128, Para. [0022]; Williams' SEQ ID NO: 128 shares 100% identity with SEQ ID NO: 148 of the instant application, and contains CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, CDRL3 of SEQ ID NO: 113), and three heavy chain CDRs comprising CDRH1 of SEQ ID NO: 108, CDRH2 of SEQ ID NO: 154, and CDRH3 of SEQ ID NO: 110 (the invention provides an isolated antibody or antigen binding fragment thereof that binds to human TIGIT comprising ...a light chain variable region comprising SEQ ID NO:132, Para. [0022]; Williams' SEQ ID NO: 132 shares 100% identity with SEQ ID NO: 152 of the instant application, and contains CDRH1 of SEQ ID NO: 108, CDRH2 of SEQ ID NO: 154).

Regarding Claim 3, modified Williams discloses the formulation of claim 1. Williams further discloses wherein the anti-TIGIT antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising SEQ ID NO: 148 (the invention provides an isolated antibody or antigen binding fragment thereof that binds to human TIGIT comprising a heavy chain variable region comprising SEQ ID NO:128, Para. [0022]; Williams' SEQ ID NO: 128 shares 100% identity with SEQ ID NO: 148 of the instant application) and a light chain variable region comprising SEQ ID NO: 152 (the invention provides an isolated antibody or antigen binding fragment thereof that binds to human TIGIT comprising ...a light chain variable region comprising SEQ ID NO:132, Para. [0022]; Williams' SEQ ID NO: 132 shares 100% identity with SEQ ID NO: 152 of the instant application, and contains CDRH1 of SEQ ID NO: 108, CDRH2 of SEQ ID NO: 154).

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Supplemental Box

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

Continuation of:

Regarding Claim 4, modified Williams discloses the formulation of claim 3. Williams further discloses wherein the anti-TIGIT antibody comprises (i) a human heavy chain IgG1 constant domain comprising the amino acid sequence of SEQ ID NO:291 (and each heavy chain comprises ...a human IgG1 constant region (SEQ ID NO:86, Para. [0053]; Williams' SEQ ID NO: 86 shares 100% identity with SEQ ID NO: 291 of the instant application) and a human kappa light chain constant domain comprising the amino acid sequence of SEQ ID NO:293 (the antibody or antigen binding fragment thereof of the invention comprises a human kappa light chain constant domain comprising the amino acid sequence of SEQ ID NO: 56, Para. [0052]; Williams' SEQ ID NO 56 shares 100% identity with SEQ ID NO: 293 of the instant application).

Claims 1-4 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.