

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

**BILL T. STOREY
ALEXION PHARMACEUTICALS, INC.
ATTN.: LEGAL - INTELLECTUAL
PROPERTY DEPT.,
100 COLLEGE STREET
NEW HAVEN, CT 6510
UNITED STATES OF AMERICA**

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing

(day/month/year)

01 July 2024 (01.07.2024)

Applicant's or agent's file reference

0638WO

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US2023/082295

International filing date (day/month/year)

04 December 2023 (04.12.2023)

Priority date (day/month/year)

05 December 2022 (05.12.2022)

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

IPC: **C07K 14/705** (2023.01); **C12N 15/864** (2023.01)

CPC: **C07K 14/70575; C12N 15/86; C07K 2319/30; C12N 2750/14143**

Applicant

ALEXION PHARMACEUTICALS, INC.

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**

Date of completion of this opinion

16 May 2024 (16.05.2024)

Authorized officer

MATOS, Taina

Facsimile No. **571-273-8300**

Telephone No. **571-272-4300**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2023/082295

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(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.
 - b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
 - ☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2023/082295

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. See claims listed below

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. 6-39 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 6-39 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. 6-40

- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a).
 - ☐ 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:

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 examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-5 are drawn to fusion proteins.

Group II+: claim 40 are drawn to polypeptide linkers.

The first invention of Group I+ is restricted to an Ig Fc domain mutation selected to be N434H and a TACI ECD portion selected to be SEQ ID NO: 1 and fusion proteins comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed Ig Fc domain mutation species and TACI ECD portion species presented in the claims (see claims 1 and 4). It is believed that claims 1-5 read on this first named invention and thus these claims will be searched without fee to the extent that they read on an Ig Fc domain mutation selected to be N434H and a TACI ECD portion selected to be SEQ ID NO: 1.

The first invention of Group II+ is restricted to an amino acid sequence selected to be SEQ ID NO: 4 and polypeptide linker comprising the same.

Applicant is invited to elect additional Ig Fc domain mutations and TACI ECD portions and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be an Ig Fc domain mutation selected to be Y436L and a TACI ECD portion selected to be SEQ ID NO: 2 and fusion proteins comprising the same. Additional Ig Fc domain mutations and TACI ECD portions and their respective, corresponding, SEQ ID NOs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on 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/examined.

The inventions listed in 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:

The Groups I+ and II+ formulas do not share a significant structural element responsible for fusion proteins and polypeptide linkers requiring the selection of alternative Ig Fc domain mutations and TACI ECD portions and amino acid sequences where “wherein the Ig Fc domain comprises one or more mutations selected from the group consisting of N434H, Y436L, L234F/L235E, M252Y/S254T/T256E, L234F/L235E/N434H, L234F/L235E/N434H, M252Y/S254T/T256E/N434H, L234F/L235E/M252Y/S254T/T256E, L234F/L235E/M252Y/S254T/T256E/N434H, and T307A/E380A/N434, and combinations thereof” and “wherein the TACI ECD portion comprises the amino acid sequence set

Box No. IV Lack of unity of invention

forth in SEQ ID NO: 1 or 2” and “A polypeptide linker comprising an amino acid sequence set forth in any one of SEQ 5 ID NOS: 4, 5, and 6.”

The special technical features of Group I+, fusion proteins, are not present in Group II+; the special technical features of Group II+, polypeptide linkers, are not present in Group I+.

Additionally, even if Groups I+ and II+ were considered to share the technical features of a fusion protein comprising a TACI extracellular domain (ECD) portion and a hybrid IgG Fc domain, wherein the Ig Fc domain comprises one or more mutations; and a polypeptide linker comprising an amino acid sequence. However, these shared technical features do not represent a contribution over the prior art.

WO 02/094852 A2 to Zymogenetics, Inc. (hereinafter, “Zymogenetics”) teaches a fusion protein comprising a TACI extracellular domain (ECD) portion (a TACI-immunoglobulin fusion protein comprises a TACI receptor moiety...a TACI receptor moiety is a portion of the extracellular domain of the TACI receptor; Pg. 10, Lns. 5-9) and a hybrid IgG Fc domain, wherein the Ig Fc domain comprises one or more mutations (the immunoglobulin moiety...a modified human IgG1 Fc was generated for creating Fc fusion proteins...replace the cysteine with a serine residue; Pg. 16, Lns. 32-37; Pg. 17, Ln 1); a polypeptide linker comprising an amino acid sequence (a peptide linker; Pg. 12, Lns. 12-17; wherein peptides comprise an amino acid sequence)

US 2019/0269787 A1 to Hanmi Science Co., Ltd. (hereinafter, “Hanmi”) teaches hybrid IgG Fc domain (aglycosylated IgG2 Fc and IgG4 fragments, combinations thereof and hybrids thereof; Para. [0053]).

The inventions listed in Groups I+ and II+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

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. 1-5

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2023/082295

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	1-5	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-5	NO
Industrial applicability (IA)	Claims	1-5	YES
	Claims	None	NO

2. Citations and explanations:

----- EXPLANATION -----

Claims 1-5 have been analyzed subject to the restriction that the claims read on an Ig Fc domain mutation selected to be N434H and a TACI ECD portion selected to be SEQ ID NO: 1 and fusion proteins comprising the same.

Claims 1-5 lack an inventive step under PCT Article 33(3) as being obvious over WO 2021/226553 to Alpine Immune Sciences Inc. (hereinafter, "Alpine") in view of US 2010/0166741 to Kelley et al. (hereinafter, "Kelley").

Regarding Claim 1, Alpine discloses a fusion protein (the immunomodulatory protein comprises a BIM attached to an immunoglobulin Fc, yielding an immunomodulatory Fc fusion; Para. [0478]) comprising a TACI extracellular domain (ECD) portion (the immunomodulatory protein comprises a BIM; Para. [0478]; the BIM is or contains a wild-type TACI ECD; Para. [0334]) and a hybrid IgG Fc domain (attached to an immunoglobulin Fc; Para. [0478]; the Fc is derived from IgG4...the IgG4 Fc is a stabilized Fc in which the CH3 domain of human IgG4 is substituted with the CH3 domain of human IgG1; Para. [0484]), wherein the IgG Fc domain comprises one or more mutations selected from the group consisting of 434 (a variant Fc region comprising one or more amino acid substitutions...such Fc variants include those with substitutions at...434...e.g. substitution of Fc region 434; Para. [0490]); and the TACI ECD portion comprises SEQ ID NO: 1 (the BIM comprises the sequence set forth in SEQ ID NO: 528; Para. [0391]; wherein SEQ ID NO: 528 is 100% identical to Applicant's SEQ ID NO: 1).

Alpine fails to explicitly disclose wherein the IgG Fc domain comprises one or more mutations selected from the group consisting of N434H.

Kelley teaches wherein the IgG Fc domain comprises one or more mutations selected from the group consisting of N434H (the anti-BR3 antibody further comprises altered Fc sequences that increase FcRn binding relative to wild-type Fc sequences selected from the group of...N434H; Para. [0008]; mutations in the Fc region...improved FcRn binding compared to native IgG; Para. [0403]; the Fc receptor mutation is a substitution...the substitution is a 434 residue of...N434H; Para. [0404]).

It would have been obvious to one of ordinary skill in the art before the priority date to modify Alpine with the IgG Fc domain comprises one or more mutations selected from the group consisting of N434H of Kelley for the purpose of improving the FcRn binding of the IgG Fc domain (Kelley; Paras. [0008], [0403]).

Regarding Claim 2, modified Alpine discloses the fusion protein of claim 1, wherein the TACI ECD portion comprises a TACI DR2 portion (the BIM comprises the sequence set for in SEQ ID NO: 528; Para. [0391]; wherein SEQ ID NO: 528 is 100% identical to Applicant's SEQ ID NO: 1, wherein Applicant's SEQ ID NO: 1 includes a TACI DR2 portion).

Regarding Claim 3, modified Alpine discloses the fusion protein of claim 2, wherein the TACI ECD portion further comprises a TACI DR1 portion (the BIM comprises the sequence set for in SEQ ID NO:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2023/082295

Box No. V

**Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability;
citations and explanations supporting such statement**

528; Para. [0391]; wherein SEQ ID NO: 528 is 100% identical to Applicant's SEQ ID NO: 1, wherein Applicant's SEQ ID NO: 1 includes a TACI DR1 portion).

Regarding Claim 4, modified Alpine discloses the fusion protein of any of the preceding claims, wherein the TACI ECD portion comprises the amino acid sequence set forth in SEQ ID NO: 1 (the BIM comprises the sequence set for in SEQ ID NO: 528; Para. [0391]; wherein SEQ ID NO: 528 is 100% identical to Applicant's SEQ ID NO: 1).

Regarding Claim 5, modified Alpine discloses the fusion protein of claim 4, wherein the TACI ECD portion consists of the amino acid sequence set forth in SEQ ID NO: 1 (the BIM comprises the sequence set for in SEQ ID NO: 528; Para. [0391]; wherein SEQ ID NO: 528 is 100% identical to Applicant's SEQ ID NO: 1).

Claims 1-5 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.