

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 0467WO	FOR FURTHER ACTION See item 4 below	
International application No. PCT/US2024/021544	International filing date (<i>day/month/year</i>) 26 March 2024 (26.03.2024)	Priority date (<i>day/month/year</i>) 02 May 2023 (02.05.2023)
International Patent Classification (IPC) or national classification and IPC See relevant information in Form PCT/ISA/237		
Applicant ALEXION PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
- In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	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 Article 35(2) 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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

	Date of issuance of this report 30 October 2025 (30.10.2025)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Simin Baharlou e-mail pct.team9@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: BILL T. STOREY
ALEXION PHARMACEUTICALS, INC.
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Date of mailing
(day/month/year)

SEP 03 2024

Applicant's or agent's file reference
0467WO

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US2024/021544

International filing date (day/month/year)

26 March 2024 (26.03.2024)

Priority date (day/month/year)

02 May 2023 (02.05.2023)

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

IPC - INV. A61K 38/46; A61P 19/08 (2024.01)

ADD. A61P 21/00 (2024.01)

CPC - INV. A61K 38/465; A61P 19/08

ADD. A61P 21/00; C07K 2319/20; C07K 2319/30; C07K 2319/33; C12Y 301/03001

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

Date of completion of this opinion

12 August 2024 (12.08.2024)

Authorized officer

Shane Thomas
PCT Help Desk
Telephone No. 571-272-4300

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2024/021544

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 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/US2024/021544

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. 5-60

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. 5-60 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 5-60 are dependent claims and 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. 5-60

☐ 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.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2024/021544

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 must be paid.

Group I+: claims 1-4, 61-68, SEQ ID NO: 21 (fusion protein sequence), are directed to a method for treating muscle weakness with peptide having alkaline phosphatase activity.

The methods of Claims 1-4, 61-62 (each in-part), and 63-68 are believed to encompass the first named invention of Groups I+ and are the claims that will be searched to the extent that they comprise a polypeptide encompassing SEQ ID NO: 21 (first exemplary fusion protein sequence). This first named invention of Group I+ has been selected to encompass the first species of each of the genera found in claims 61-62 are based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines.

Applicant is invited to elect additional sequences, where available as an option within at least one searchable claim, to be searched. Additional sequence(s) will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected sequence(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/examined. An exemplary election would be SEQ ID NO: 22 (fusion protein sequence).

Groups I+ share the technical features including: a method of treating or reducing the risk of developing muscle weakness in a subject having or at risk of having a muscle weakness disease comprising administering to the subject a therapeutically effective amount of at least one recombinant polypeptide having alkaline phosphatase activity, wherein the subject exhibits a reduced concentration of tissue non-specific alkaline phosphatase "TNSALP", and wherein the subject does not have a loss-of-function mutation in an ALPL gene.

However, these shared technical features are previously disclosed by WO 2017/173413 A1 to Alexion Pharmaceuticals Inc. (hereinafter "Alexion").

Alexion discloses a method of treating or reducing the risk of developing muscle weakness in a subject having or at risk of having a muscle weakness disease comprising administering to the subject a therapeutically effective amount of at least one recombinant polypeptide having alkaline phosphatase activity (muscle weakness disease treated in subject with recombinant polypeptide having alkaline phosphatase activity; abstract), wherein the subject exhibits a reduced concentration of tissue non-specific alkaline phosphatase "TNSALP", and wherein the subject does not have a loss-of-function mutation in an ALPL gene (subjects can be administered composition with disease CPPD; page lines; Note: present PCT application defines subjects with CPPD as eligible for receiving treatment and would thereby fall under the definition of not having a loss of function ALPL gene; page 6, lines 20-22).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Alexion reference, unity of invention is lacking.

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. Group I+: claims 1-4, 61-68, SEQ ID NO: 21 (fusion protein sequence).

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2024/021544

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	4, 67-68	YES
	Claims	1-3, 61-66	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-4, 61-68	NO
Industrial applicability (IA)	Claims	1-4, 61-68	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-3, and 61-66 lack novelty under PCT Article 33(2) as being obvious over US 2021/0169994 A1 to Alexion Pharmaceuticals, Inc (Hereinafter 'AP'994').

As per claim 1, AP'994 discloses a method of treating or reducing the risk of developing muscle weakness in a subject having or at risk of having a muscle weakness disease comprising administering to the subject a therapeutically effective amount (The polypeptide may be administered in an amount and for a duration sufficient to treat the disease or to alleviate one or more symptoms thereof, The treating may enhance bone formation in the subject. The polypeptide may be used to treat muscle weakness; paragraph [0031]) of at least one recombinant polypeptide having alkaline phosphatase activity, wherein the subject exhibits a reduced concentration of tissue non-specific alkaline phosphatase 'TNSALP' (Administration of the recombinant polypeptide which has alkaline phosphatase activity, may promote a median increase in ALP concentration in a plasma sample from the subject, such diseases such as HPP refer to a rare, heritable skeletal disorder caused by, e.g., one or more loss-of-function mutations in the ALPL 'alkaline phosphatase, liver/bone/kidney' gene, which encodes tissue-nonspecific alkaline phosphatase 'TNSALP', which would be reduced in the subject; paragraph [0039], [0060]), and wherein the subject does not have a loss-of-function mutation in an ALPL gene (Administration of the recombinant polypeptide, wherein not stated to have a mutation in the ALPL gene; paragraph [0039]).

As per claim 2, AP'994 discloses the method of claim 1, and AP'994 further discloses wherein the reduced concentration of TNSALP is caused by reduced transcription of ALPL, reduced translation of ALPL mRNA, elevated or reduced posttranslational modification of TNSALP, or reduced of TNSALP enzymatic activity (Administration of the recombinant polypeptide which has alkaline phosphatase activity, may promote a median increase in ALP concentration in a plasma sample from the subject, such diseases such as HPP refer to a rare, heritable skeletal disorder caused by, e.g., one or more loss-of-function mutations in the ALPL 'alkaline phosphatase, liver/bone/kidney' gene, which encodes tissue-nonspecific alkaline phosphatase 'TNSALP', which would be reduced in the subject; paragraph [0039], [0060]).

As per claim 3, AP'994 discloses the method of claim 1 or 2, and AP'994 further discloses wherein the reduced transcription of ALPL, reduced translation of ALPL mRNA, elevated or reduced posttranslational modification of TNSALP, or reduced TNSALP enzymatic activity is measured relative to a normal subject (Administration of the recombinant polypeptide which has alkaline phosphatase activity, may promote a median increase in ALP concentration in a plasma sample from the subject, such diseases such as HPP refer to a rare, heritable skeletal disorder caused by, e.g., one or more loss-of-function mutations in the ALPL 'alkaline phosphatase, liver/bone/kidney' gene, which encodes tissue-nonspecific alkaline phosphatase 'TNSALP', which would be reduced in the subject; paragraph [0039], [0060]).

As per claim 61, AP'994 discloses the method of claim 1, and AP'994 further discloses wherein the recombinant polypeptide comprises a fusion protein comprising an amino acid comprising at least 95% sequence identity to SEQ ID NO: 21 (SEQ ID NO:123 of AP'994 is 100% identical to SEQ ID NO:21 of the Instant PCT application from residues 1-724; paragraph [0329]).

As per claim 62, AP'994 discloses the method of claim 61, and AP'994 further discloses wherein the recombinant polypeptide comprises a fusion protein comprising an amino acid sequence of SEQ ID NO: 21 (SEQ ID NO:123 of AP'994 is 100% identical to SEQ ID NO:21 of the Instant PCT application from residues 1-724; paragraph [0329]).

As per claim 63, AP'994 discloses the method of claim 1, and AP'994 further discloses wherein: the recombinant polypeptide comprises an immunoglobulin molecule, the immunoglobulin molecule is An IgG2/4 fragment crystallizable 'Fc' region (A polypeptide comprising an alkaline phosphatase and a fragment crystallization 'Fc' region, wherein the Fc region is an IgG2/4 chimera.; Claim 49), and the Fc comprises an amino acid sequence of SEQ ID NO: 21 (SEQ ID NO:123 of AP'994 is 100% identical to SEQ ID NO:21 of the Instant PCT application from residues 1-724; paragraph [0329]).

As per claim 64, AP'994 discloses the method of claim 61, and AP'994 further discloses wherein the administration of the therapeutically effective amount is biweekly (In particular, the sALP can be administered one or more times per week, one or more times every other week, which would be biweekly; paragraph [0178]).

As per claim 65, AP'994 discloses the method of claim 61, and AP'994 further discloses wherein the administration of the therapeutically

----Continued in Supplemental Box----

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2024/021544

Supplemental Box

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

-Continued From Box V. 2: Citations and Explanations-

effective amount is from about 0.1 mg/kg to about 20 mg/kg (A pharmaceutical formulation containing the polypeptide of SEQ ID NO: 123 can be formulated at 0.5 mg/kg; paragraph [0329]).

As per claim 66, AP'994 discloses the method of claim 65, and AP'994 further discloses wherein muscle weakness disease comprises: muscular dystrophy, myasthenia gravis, and calcium pyrophosphate deposition disease 'CPPD' (The subject may have a muscle weakness disease, such as calcium pyrophosphate deposition 'CPPD' or familial hypophosphatemia; paragraph [0186]).

Claim 4 lacks an inventive step under PCT Article 33(3) as being obvious over AP'994 in view of the publication entitled "New mouse models for metabolic bone diseases generated by genome-wide ENU mutagenesis" by Sabrautzki, S. et al. (hereinafter "Sabrautzki").

As per claim 4, AP'994 discloses the method of any one of claims 1 to 3, but AP'994 does not disclose wherein the subject has a mutation in a 3' untranslated region 'UTR', a 5' UTR, or an intronic region of the ALPL gene. Sabrautzki discloses wherein the subject has a mutation in a 3' untranslated region 'UTR', a 5' UTR, or an intronic region of the ALPL gene (mice mutants made with mutations in intron 9 of ALPL; page 423, 2nd column, 1st paragraph). It would have been obvious to a person of ordinary skill in the art, before the relevant date, to have modified the mutation of AP'994 to have incorporated intronic region mutation, as disclosed by Sabrautzki, because when introns of the ALPL gene was mutated at the intron 9, alkaline phosphatase demonstrated reduced activity and would be an obvious mutation in a subject with HPP for targeted treatment (Sabrautzki; Table 1).

Claim 67 lacks an inventive step under PCT Article 33(3) as being obvious over AP'994 in view of WO 2017/173413 A1 to Alexion Pharmaceuticals Inc. (hereinafter 'Alexion').

As per claim 67, AP'994 discloses the method of claim 61, but AP'994 does not disclose wherein the administration improves mitochondrial bioenergetics in skeletal muscle fibers. Alexion discloses wherein the administration improves mitochondrial bioenergetics in skeletal muscle fibers (Recently, asfotase alfa, a recombinant bone-targeted human TNASLP has been reported to decrease the elevated inorganic pyrophosphate concentration and improved skeletal mineralization, growth which would include skeletal muscle fibers from inherited mitochondrial bioenergetics; Page 21, Lines 3-6). It would have been obvious to a person of ordinary skill in the art, before the relevant date, to have modified the method of AP'994 to have incorporated wherein administration improves mitochondrial bioenergetics in skeletal muscle fibers as disclosed by Alexion, because this would improve the biological functions which leads to skeletal muscle fiber improvement.

Claim 68 lacks an inventive step under PCT Article 33(3) as being obvious over AP'994 in view of WO 2022/232169 A1 to UNIVERSITY OF MASSACHUSETTS. Et al (Hereinafter 'UM').

As per claim 68, AP'994 discloses the method of claim 1, and AP'994 further discloses wherein the treatment with the therapeutically effective amount of the at least one recombinant polypeptide having the alkaline phosphatase activity (Administration of the recombinant polypeptide which has alkaline phosphatase activity, may promote a median increase in ALP concentration in a plasma sample from the subject; paragraph [0039]), but AP'994 does not disclose a decrease in a level of valine, leucine, or isoleucine in a muscle of the subject. UM discloses a decrease in a level of valine, leucine, or isoleucine in a muscle of the subject (the method 'e.g., administration of the isolated nucleic acid, rAAV, or compositions of the present disclosure' increases the degradation of the branched chain amino acids 'BCAA; leucine, isoleucine, and valine'; paragraph [0155]). It would have been obvious to a person of ordinary skill in the art, before the relevant date, to have modified the method of AP'994 to have incorporated a decrease in a level of valine, leucine, or isoleucine as disclosed by UM, because the invention would benefit from decreasing associated amino acids, which would improve the functionality in muscles targeted.

Claims 1-4, 61-68 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.