

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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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/EP2023/065930

International filing date (day/month/year)
14.06.2023

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15.06.2022

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/47 A61K38/17 C07K16/18 A61K38/00

Applicant
UCB BIOPHARMA SRL

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

Authorized Officer

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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.
 - 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:

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	<u>4, 6, 7, 10</u>
	No: Claims	<u>1-3, 5, 8, 9, 11-16</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-16</u>
Industrial applicability (IA)	Yes: Claims	<u>1-16</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

1 **Re Item V**

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

1.1 Reference is made to the following documents, the numbering will be adhered to in the rest of the procedure:

- D1 US 2016/311874 A1 (KUMAR RAVINDRA [US] ET AL) 27 October 2016 (2016-10-27)
- D2 WO 2020/011868 A1 (UCB BIOPHARMA SRL [BE]) 16 January 2020 (2020-01-16)
- D3 MAESHIMA AKITO ET AL: "Follistatin, an Activin Antagonist, Ameliorates Renal Interstitial Fibrosis in a Rat Model of Unilateral Ureteral Obstruction", BIOMED RESEARCH INTERNATIONAL, vol. 2014 1 January 2014 (2014-01-01), pages 1-10, XP093001908, ISSN: 2314-6133, DOI: 10.1155/2014/376191
Retrieved from the Internet:
URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4026945/pdf/BMRI2014-376191.pdf>
- D4 WO 2015/187977 A1 (ACCELERON PHARMA INC [US]) 10 December 2015 (2015-12-10)
- D5 US 9 879 077 B2 (APRILBIO CO LTD [KR]) 30 January 2018 (2018-01-30)

Document D1 discloses a follistatin-related fusion protein forming heteromeric protein complexes with high affinity to follistatin ligands such as activin A/B. The fusion protein is capable of inhibiting follistatin ligands, and exhibits an extended half-life (paragraph 4). The follistatin moiety is attached through a linker to one of two human IgG1 Fc chains (antibody moiety) (example 1). SEQ ID NOs 4 and 2 have complete sequence identity with SEQ ID NOs 1 and 2 of the current application.

Document D2 discloses an anti-albumin Fab antibody, namely CA645, comprising a polypeptide within the framework 3 region of the V domain (Example 1). SEQ ID NOs 6 and 1 have 100% sequence identity with SEQ ID NOs 5 and 6 of the current application, respectively.

Document D3 is a research article disclosing the role of follistatin in improving renal interstitial fibrosis in a rat model of unilateral ureteral obstruction (title, abstract).

Document D4 discloses follistatin polypeptides that are capable of inhibiting follistatin ligands in proximity to the administration site, while having little systemic effect on the patients (paragraph 4). The polypeptides are designed to dimerize and comprise a portion of an immunoglobulin constant domain from human IgG (paragraph 5, example 1).

Document D5 discloses an anti-serum albumin Fab-effector moiety (title), namely SL335, in a Fab-fusion protein construct (column 1). SL335 Fab was shown to provide increased half-life (column 4). Example 2.4 discloses SL335-hGH fusion polypeptides.

1.2 Novelty (Article 33 (2) PCT)

- 1.2.1 Document D1 discloses a follistatin-related fusion protein, forming heteromeric protein complexes with high affinity to follistatin ligands, such as activin A/B. The fusion protein is capable of inhibiting follistatin ligands, and exhibits an extended half-life and improved purification properties (paragraph 4). Example 1 discloses full-length human WFFIKKN2 (follistatin variant)-Fc fusion proteins, comprising a linker (paragraph 6, SEQ ID NO 57). Furthermore, SEQ ID NOs 4 and 2 have 100% sequence identity with SEQ ID NOs 1 and 2 of the current application, respectively. SEQ ID NO: 2 has 99% sequence identity with SEQ ID NO: 4 of the current application, while SEQ ID NO: 4 has 99% sequence identity with SEQ ID NO: 3 of the current application. The follistatin moiety is disclosed to be positioned either C- or N-terminally to the antibody moiety (paragraph 22). Moreover, D1 discloses production methods of the fusion proteins (paragraphs 137-144) and a pharmaceutical composition comprising the follistatin-related fusion protein (paragraph 163). The follistatin-related fusion proteins are disclosed for use in the treatment of neuromuscular disorders and neurodegenerative diseases (paragraph 149). Hence, D1 discloses the subject-matter of claims 1-3, 5, 8-9 and 11-16, and therefore these claims cannot be considered novel under Article 33 (2) PCT.

- 1.2.2 The subject-matter of claims 4 and 6, namely a follistatin fusion protein with an antibody (Fab) moiety binding albumin has not previously been disclosed. Hence, the subject-matter of claims 4 and 6, is considered new under Article 33 (2) PCT.
- 1.2.3 Since the subject-matter of claims 4 and 6 is considered novel, claim 7 further disclosing the CDR sequences of the antibody moiety of the fusion protein, is also considered novel under Article 33 (2) PCT. Similarly, the subject-matter of claim 10, namely the sequences of both the follistatin moiety and the Fab heavy and light chains in combination, has not previously been disclosed and is considered novel under Article 33 (2) PCT.

1.3 Inventive Step (Article 33 (3) PCT)

- 1.3.1 Claims 1-3, 5, 8-9 and 11-16 are not considered novel under Article 33 (2) PCT and therefore cannot involve an inventive step under Article 33 (3) PCT.

Document D1 is regarded as being the prior art closest to the subject-matter of claim 4, as it discloses a follistatin-related fusion protein with serum albumin or an Fc (paragraph 101), which are both known to increase serum half-life.

The technical difference between the current application and the closest prior art may be seen as the follistatin-fusion protein comprising an antibody moiety binding albumin, while D1 discloses a direct fusion of the polypeptide to serum albumin or an Fc (paragraph 101).

No technical effect arising from the aforementioned technical difference may be described, as both polypeptide fusion to an anti-albumin antibody (example 2 of current application) or to an Fc (example 2 in D1) lead to improved pharmacokinetic properties, such as extended half-life.

Hence, the objective technical problem to be solved may be regarded as the provision of an alternative follistatin-fusion protein suitable for use in therapy.

The solution to the above-mentioned problem to be solved is a fusion protein comprising a follistatin moiety and an antibody moiety binding albumin, as disclosed in claim 4 of the current application.

As previously described, D1 discloses a follistatin fusion protein comprising a

human Fc-portion, which was shown to have half-life extending properties (example 1, paragraph 4). Additionally, document D2 teaches an antibody comprising a variable (V) domain and an insert polypeptide, wherein the insert polypeptide is within the framework 3 region of the V domain (page 2). Specifically, an anti-human serum albumin Fab antibody is disclosed, namely CA645 (example 1), fused to an IL-15 polypeptide (Figure 2B). Furthermore, the light chain and heavy chain (SEQ ID NOs 1 and 6) are identical to SEQ ID NOs 6 and 5 of the current application, respectively. D2 also discloses the purpose of the disclosed Fab antibody to be improved pharmacokinetics, including serum half-life extension (page 2). In light of the combined teachings of documents D1 and D2, the proposed solution, namely the provision of a further follistatin fusion protein comprising an anti-albumin antibody cannot be considered inventive. The person skilled in the art would, based on the available common knowledge, have a reasonable expectation of success in improving half-life when fusing both follistatin and antibody moiety against albumin.

The subject-matter of claim 4 is therefore not considered inventive under Article 33 (3) PCT.

- 1.3.2 The subject-matter of claim 6 discloses the antigen-binding moiety being a Fab, a Fab', or a F(ab')₂. While this technical feature is lacking in the closest prior art document D1, it is disclosed in D2 (see example 1 and Figure 2B). As described above, the person skilled in the art would not require an inventive step to combine the teachings from document D1 and D2 to arrive at the subject-matter of claim 6.
- 1.3.3 Claim 7 discloses the CDR sequences of the anti-albumin Fab moiety, namely SEQ ID NOs 13-18. Since light and heavy chain variable regions have already been disclosed in D2, the subject-matter of claim 7 is not considered inventive under Article 33 (3) PCT.
- 1.3.4 The subject-matter of claim 10 further discloses the sequences of both follistatin and Fab moieties of the fusion protein in combination (SEQ ID NOs 1-3 and 5-6). As previously discussed above, the sequences have previously been disclosed in D1 and D2, respectively, and cannot be considered inventive in combination.
- 1.3.5 In summary, in light of the prior art documents D1 and D2, the subject-matter of claims 4, 6-7 and 10 is not considered inventive under Article 33 (3) PCT.

2 **Re Item VIII**

Certain observations on the international application

2.1 **Clarity (Article 6 PCT)**

- 2.1.1 The application does not meet the requirement of Article 6 PCT due to objections to claims 6 and 7, as described below:
- 2.1.2 Claim 6 in its current form states "*a Fab, a Fab?, or a F(ab')₂*", which should be corrected to a Fab, a Fab', or a F(ab')₂.
- 2.1.3 Claim 7 discloses the light chain variable region and heavy chain variable region to comprise "*at least one CDR*". The structural definition of an antibody is defined through the six CDRs, and any fewer than six CDRs would lead to a lack of essential technical features.