

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/EP2019/070628	International filing date (day/month/year) 31.07.2019	Priority date (day/month/year) 01.08.2018
International Patent Classification (IPC) or both national classification and IPC INV. C07K16/36 C07K16/40 C07K16/46 A61P7/04		
Applicant NOVO NORDISK A/S		

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:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Turri, Matteo Telephone No. +49 89 2399-0
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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:
 - ☒ 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 13ter.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 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.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:

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>2-14, 18</u>
	No: Claims	<u>1, 15-17</u>
Inventive step (IS)	Yes: Claims	<u>12, 13, 18</u>
	No: Claims	<u>1-11, 14-17</u>
Industrial applicability (IA)	Yes: Claims	<u>1-18</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

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

1 Reference is made to the following documents:

- D1** EP 2 644 698 A1 (CHUGAI PHARMACEUTICAL CO LTD [JP]) 2 October 2013 (2013-10-02) cited in the application
- D2** ZENJIRO SAMPEI ET AL: "Identification and Multidimensional Optimization of an Asymmetric Bispecific IgG Antibody Mimicking the Function of Factor VIII Cofactor Activity",
PLOS ONE,
vol. 8, no. 2, 28 February 2013 (2013-02-28), page e57479, XP055553036,
DOI: 10.1371/journal.pone.0057479
cited in the application
- D3** TAKEHISA KITAZAWA ET AL: "A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model",
NATURE MEDICINE,
vol. 18, no. 10, 30 September 2012 (2012-09-30), pages 1570-1574,
XP055246561,
New York
ISSN: 1078-8956, DOI: 10.1038/nm.2942
- D4** Naoki Uchida ET AL: "Plenary Paper CLINICAL TRIALS AND OBSERVATIONS A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects",
, 1 December 2015 (2015-12-01), XP055468638,
DOI: 10.1182/blood-2015-06-650226
Retrieved from the Internet:
URL: <http://www.bloodjournal.org/content/bloodjournal/127/13/1633.full.pdf?sso-checked=true>
[retrieved on 2018-04-19]

Novelty (Article 33(2) PCT)

- 2 Document **D1** discloses bispecific antibodies which binds to both FIX(a) and FX thus promoting the FX activation by FIXa (see [0008]). Also disclosed are the use of the antibodies to treat haemophilia and pharmaceutical compositions comprising them (see [0096] and [0097]).

3 Said document is considered to anticipate present **claims 1 and 15-17**.

Inventive step (Article 33(3) PCT)

4 Documents **D1-D4** all disclose the pro-coagulatory bi-specific antibody emicizumab or ACE910. This antibody is considered as the closest prior art.

5 The difference between the present application and the prior art is that further antibodies, characterized by their sequences, are provided. The effect induced by said difference is that the monovalent one armed antibodies have an increased FIXa activity as compared to the corresponding monovalent OA antibodies of the prior art (Table 14).

6 Based on said effect, the underlying technical problem can be formulated as the provision of improved pro-coagulatory bi-specific antibodies

7 This problem is solved by antibodies in which the first antigen binding site capable of binding to FIX is one of the ones listed in Table 14, for which and increased activity has been shown. The provision of such antibodies is not considered as obvious for the skilled person. An inventive step is therefore acknowledged for these antibodies, either in their monovalent form (as referred to in **claim 18**), or bivalent one in combination with the anti FX(a) specificity (as in **claims 12 and 13**).

8 The following, however, must be noticed:

9 Antibodies which compete with the above antibodies - as referred to in **claim 2** - are neither shown nor considered to solve the underlying problem as the ones for which an inventive step has been acknowledged. They are therefore not inventive.

10 Similarly, antibodies having amino acid substitutions and/or a certain degree of identity (**claim 14**) are not shown to retain the improved properties of the ones for which the improved effect as been shown and as such are also not inventive.

11 Antibodies against FX(a), as referred to in **claim 2**, are also not shown to have any improved properties. They are therefore not inventive.

12 The provision of antibodies with a desired effect (as referred to in **claim 1**) and defined by the epitope which they recognize (e.g. **claim 3**) or their paratopes (e.g. **claim 10**) is considered an undue burden for the skilled person.