PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2018/063476	23.05.2018	23.05.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/50 A61K38/19 C07K14/475 G01N33/68

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 43*bis*.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 notifed the International Bureau under Rule 66.1*bis*(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:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Landré, Julien Telephone No. +49 89 2399-0

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 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:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

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

Re Item V

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

Reference is made to the following documents:

1 **Novelty (Article 33(2) PCT).**

1.1 None of the documents of the prior art teach a MIC-1 polypeptide and an amino acid extension resulting in a polypeptide having a pI of less than 6.5.

2 **Inventive activity (Article 33(3) PCT).**

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of **claims 1-15** does not involve an inventive activity in the sense of Article 33(3) PCT.

2.2 WO2013/148117 (**D1**) is considered the closest prior art and teaches a MIC-1 polypeptide with an N-terminal amino acid extension and a protractor, here PEG, attached to the amino acid extension, wherein the amino acid extension comprises 3 to 36 amino acid residues (p. 2, li. 21-23, p. 9 li. 28-30, p. 16 li. 21-22, p. 31 li. 19, p. 35 li. 28-31, p. 37 li. 14-22, p. 59 li. 30). **D1** teaches sequences having a surplus of acidic amino acids, composed of A,C,E,G,P,S,T, being at least 10-32 amino acid residues as SEQ. ID. No. 58 is 96.7% identical to SEQ. ID. No. 223 of the present application, SEQ. ID. No. 379 is 96.7% identical to SEQ. ID. No. 224 and is 96.9% identical to SEQ. ID. No. 226 of the present application. **D1** teaches pharmaceutical compositions (p. 4 li. 8-11, p. 47 li. 10-12), linking via a cysteine (p. 29 li. 8-11), a method of production of the polypeptide (p. 41 li. 5-8), treatment of obesity (p. 46 li. 18-22).

2.3 Claim 1.

The subject matter of **claim 1** and **D1** differs in that **claim 1** uses MIC-1 polypeptide and an amino acid extension resulting in a polypeptide having a pI of less than 6.5.

The term is unclear (See RE Item VIII, 1.2) and no effect is disclosed in the application as originally filed regarding this difference.

The problem to be solved is the provision of an alternative MIC-1 polypeptide.

First, an unclear term cannot be allowed in a claim if the term is essential having regard to the invention.

Second, as mentioned below (See RE Item VIII, 1.2) only very specific sequences have been shown to display to have an effect on solubility. Therefore, the objective technical problem is not solved over the entire scope of **claim 1**.

Three partial technical problems have been identified:

1) increasing half-life of the conjugates. This is solved by the specific protractors (application p. 10, 2nd §).

2) increasing solubility. This is solved by the specific extension sequences (application p. 18, 2nd §).

3) increasing stability by decreasing oxidation. This is solved by mutating methionine (application p. 18, 6th §).

2.4 Specific protractors (Claims 2-7).

The subject matter of **claims 2-7** and **D1** differ in that **claims 2-7** uses protractors having specific structural features comprising chem. 1, chem. 2, chem. 3 and chem. 4.

The effect is that the *in vivo* circulatory half-life of the MIC-1 polypeptide (Application p. 10, 2nd §). However, this is already known in the art, as PEG as the same function (see also Application p. 10, 2nd §).

The objective technical problem was therefore to provide alternative protractors.

WO2016/149501 (**D2**) discloses a polypeptide with an N-terminal amino acid extension and a protractor attached to the amino acid extension, wherein the amino acid extension comprises 3 to 36 amino acid residues, here up to 5 ([010], [013]-[014], [042], [044], [056]) to increase the half-life of the polypeptide ([090], [0117], [0130], [0185]). **D2** teaches the polypeptide is MIC-1, here GDF-15 ([0171]), the protractor is of formula X (p. 28, 1st compound, p. 119 entry 41) and linked via the sulfur atom of a cysteine ([042], [056], [0115], [0130]). **D2** teaches vectors ([0235]), cells ([0237]),a method of production ([0238]), a pharmaceutical composition ([0213]), the use of the conjugate for the treatment of diseases such as diabetes, dyslipidemia ([0207]).

WO2015/200078 (**D3**) also a GDF-15 (i.e. MIC-1) conjugated to a protractor of formula via amino acid extension comprises 3 to 36 amino acid residues (p. 8, 5th §; p. 20, last §-p. 22, 4th §; p. 23, 3rd-4th §, p. 28-30 chemical structures; p. 35, 3rd §; p. 35, last §; p. 36 structures A and B, p. 39-41 chemical structures) to increase the half-life of the polypeptide (p. 2, 5th §). **D3** teaches a pharmaceutical composition and its use in the treatment of e.g. atherosclerosis, diabetes or obesity (p. 3, 2nd §; p. 3, 6th §; p. 4, 1st §, p. 5, last §; p. 6, 2nd §; p. 61, last §; p. 67, 1st-3rd §). **D3** also teaches a method for manufacturing the polypeptide using vectors and host cells (p. 47, 1st §; p. 50, penultimate §; p. 51, 2nd §; p. 51, penultimate §).

WO2016/102562 (**D4**) teaches protractors having specific structural features comprising chem. 1, chem. 2, chem. 3 and chem. 4 (p. 3 li. 4-p. 4 li. 12, p. 5 li. 22-p. 7 li. 8, p. 13 li. 16-p. 16 li. 20, p. 25-28 embodiments 1-9) including a compound of formula X and XIII (p. 59 chemical structure, p. 73 example 4.11, p. 101, example 5.20, p. 117 chemical structure). **D4** also teaches the attachment via a cysteine (p. 2 li. 15-19), a method of producing a polypeptide (p. 21 li. 1-9). **D4** a pharmaceutical composition and its use in the treatment of e.g. diabetes, dyslipidemia or atherosclerosis (p. 4 li. 31-p. 5 li. 2, p. 22 li. 1-3, p. 24 li. 5-19). **D4** also states that it was surprising that such modification did **not** lead to a decrease in potency (p. 122 li. 2-5, p. 123 li. 4-7).

Knowing the advantages of protractors comprising chem. 1, chem. 2, chem. 3 and chem. 4, from any of **D2-D4** independently as well as that these can be applied to increase the half-life of MIC-1 conjugates, the person skilled in the art would have had no practical difficulties in applying said teachings to the conjugates of **D1**. Therefore, the subject matter of **claims 2-7** lacks an inventive step.

2.5 Specific extensions (Claims 8-11).

The specific extension sequences and their advantage regarding solubility are known in the art (see **D1**). The only difference is a mutation of one amino acid to a cysteine for attaching the protractor. Such modification is also well known in the art (see **D2**, **D4**). Therefore, **claims 8-11** lack an inventive activity.

2.6 MIC-1 sequences (Claims 12-13).

Mutations of methionine to avoid oxidation is already known in the art such as in **D3** (p. 45, 3rd §) or Kim et al., 2001 (**D5**:Abstract, p. 344 col. 1,4th §; p. 344 col. 1, last §-p. 344 col. 2, 1st §; p. 345 col. 1, last §, p. 345 col. 2, 1st §; p. 346 col. 1, 2nd §, p. 346 col. 2, last §)

2.7 Formula 1-21 (Claim 14).

The present application provides data on the synthesis of compounds of formula 1-21. The application concluded very generally that protractors do not impact solubility (application p. 169, last §) nor the potency of the compound (p. 172 penultimate §). The application states that the latter is surprising. However, this is known in the art (see e.g. **D4**). Therefore, **claim 14** lacks an inventive activity.

2.8 Medical claim (Claim 15).

The use of MIC-1 conjugates having an increased half-life for the treatment of metabolic disorder such as obesity, diabetes, cardiovascular like dyslipidaemia, arteriosclerosis, steatohepatitis, or diabetic nephropathy is known in the art (see **D1**-**D4**). This cannot confer an inventive activity to the conjugates lacking an inventive activity.

RE Item VI. Priority

The ISA does not have in its possession a copy of the priority application. The validity of the priority claim will have to analysed once such copy of the priority application will be made available. This may have implication on certain cited documents (see RE Item VI below).

Should the priorities of the present application be found invalid, documents WO2017/202936 (**D6**) and WO2017/109706 (**D7**) would become highly relevant for novelty and inventive step.

Re Item VIII

Certain observations on the international application

1.1 The application does not meet the requirements of Article 6 PCT, because **claims 1, 8** are not clear.

1.2 **Claim 1** is unclear as the extension is very vaguely defined, i.e. "*comprises 3 to 36 amino acid residues*" and the resulting polypeptide is not defined in terms of structural features but in terms of desired properties, i.e "*the MIC-1 polypeptide with the amino acid extension has a calculated pI lower than 6.5*". The present application only teaches specific extension sequences, e.g. SEQ. ID. Nos. 223-227, 229-337 were shown to work. The application states that extensions with the 12-mers block cannot be expressed (p. 107, 1st §; p. 108, last §). Therefore, **claim 1** must be limited to the specific sequences for which an effect has been demonstrated.

1.3 **Claim 8** is unclear as it is defined in terms of result to be achieved, i.e. more acidic aa residues than basic aa residues regarding an undefined extension (see Item 1.2 above).