PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference T75093WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2020/074134	International filing date *(day/month/year)* 28 August 2020 (28.08.2020)	Priority date *(day/month/year)* 30 August 2019 (30.08.2019)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant 4TEEN4 PHARMACEUTICALS GMBH		

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 8 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 or 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 44*bis*.3(c) and 93*bis*.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 44*bis* .2).

	Date of issuance of this report 01 March 2022 (01.03.2022)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nora Lindner e-mail pct.team5@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

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/EP2020/074134	28.08.2020	30.08.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61P9/00 G01N33/48 A61K38/08 A61K38/22 A61K39/395 A61K45/06

Applicant
4TEEN4 PHARMACEUTICALS GMBH

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	Bochelen, Damien Telephone No. +49 89 2399-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2020/074134

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. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

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	14-16, 18-24
	No:	Claims	1-13, 17, 25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-25
	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 II

Priority

1 The claimed priority date is valid.

Re Item V

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

2 Prior art:

Reference is made to the following documents:

D1 KOJI TAKAGI ET AL: "Circulating dipeptidyl peptidase 3 and alteration in haemodynamics in cardiogenic shock: results from the OptimaCC trial", EUROPEAN JOURNAL OF HEART FAILURE, vol. 22, no. 2, 31 August 2019 (2019-08-31), pages 279-286, XP055681198, NL ISSN: 1388-9842, DOI: 10.1002/ejhf.1600

D2 LINDA REHFELD ET AL: "Novel Methods for the Quantification of Dipeptidyl Peptidase 3 (DPP3) Concentration and Activity in Human Blood Samples", THE JOURNAL OF APPLIED LABORATORY MEDICINE, vol. 3, no. 6, 1 May 2019 (2019-05-01), pages 943-953, XP055681701, ISSN: 2576-9456, DOI: 10.1373/jalm.2018.027995

D3 ESTEVÃO BASSI ET AL: "Therapeutic Strategies for High-Dose Vasopressor-Dependent Shock", CRITICAL CARE RESEARCH AND PRACTICE, vol. 2013, 1 January 2013 (2013-01-01), pages 1-10, XP055681557, ISSN: 2090-1305, DOI: 10.1155/2013/654708

D4 WO 2019/077082 A1 (ADRENOMED AG [DE]) 25 April 2019 (2019-04-25)

D5 JADHAV AMAR P ET AL: "Angiotensin II in septic shock", AMERICAN JOURNAL OF EMERGENCY MEDICINE, vol. 37, no. 6, 19 March 2019 (2019-03-19), pages 1169-1174, XP085707434, ISSN: 0735-6757, DOI: 10.1016/J.AJEM.2019.03.026

If not indicated otherwise the relevant passages are those mentioned in the search report.

Document D1 discloses that circulating DPP3 is increased in patients with refractory cardiogenic shock despite vasopressor treatment, compared to patients having non-refractory shock.

Document D2 discloses a method for assessing circulatory DPP3 in patients with severe sepsis and septic shock and shows that DPP3 levels increase with the severity and the mortality risk.

Document D3 discloses the use of vasopressors e.g. arginine vasopressin for the treatment of refractory shock.

Document D4 discloses the assessment of pro-adrenomedullin fragment for determining the outcome of the treatment with anti-adrenomedullin antibody or antibody-fragment.

Document D5 discloses the use of angiotensin II in the treatment of septic shock.

3 Novelty (Art. 33 (1) and (2) PCT):

3.1 Document D2 does not explicitly disclose that the DPP3 level is compared to a predetermined threshold. However, it is considered that implicitly D2 compares the DPP3 levels with values of DPP3 levels in healthy subjects or shock vs refractory shock patients. Furthermore, it is noted that this threshold is not defined in the claims and it is thus not possible to determine whether the DPP3 levels are above a threshold (see point 6 below). Therefore, it is considered that the disclosure of D2 anticipates the subject-matter of claims 1 and 25. The dependent claims 2-4 lack also novelty in view of D2. Claims 5-10 are directed to a method of diagnosis and comprise a step which is a method of treatment

(see point 7 below) which renders the scope of the claims unclear. It is considered that this second part relating to a treatment is not a characterizing feature. Claims 5-12 lack thus novelty.

3.2 Claims 13 and 17 are directed to a vasopressor for use in the treatment of patients identified by a method of claim 1 wherein the DPP3 level is below an undefined predetermined threshold. D3 discloses the use of vasopressors e.g. arginine vasopressin for the treatment of refractory shock. It appears that the group of patients identified by the method of claim 1 does not differ from the patients of D3 which have refractory shock. Claim 13 and 17 lack novelty in view of D3.

Claims 1-13, 17 and 25 do not meet the requirements of Art.33(2) PCT.

4 Inventive step (Art. 33 (1) and (3) PCT):

4.1 Document D2 which is the closest prior art for claims 14 and 18 discloses that circulatory DPP3 in patients with severe sepsis and septic shock increases with the severity and the mortality risk. Claims 14 and 18 differ in that the DPP3 inhibitor is used in patients identified by measuring DPP3 levels i.e. having refractory shock. The problem to be solved is defined as to provide a treatment for refractory shock. The application does not provide any evidence that refractory shock is useful for treating patients having refractory shock. The problem is thus not solved. In view of D2 showing that DPP3 levels increase with the severity of the symptoms in septic shock patients, it would be obvious for a skilled person to consider the use of a DPP3 inhibitor to solve the problem. Claims 14 and 18 are not inventive.

4.2 The dependent claims 15-16 and 19-21 differ in that the DPP3 inhibitor is combined with an angiotensin-receptor-agonist like angiotensin II. The problem to be solved is defined as to provide an improved treatment for refractory shock. The application does not provide any evidence of an unexpected technical effect due to the claimed combinations. The problem is thus redefined as to provide an alternative treatment for refractory shock. Vasopressors e.g. angiotensin II, are known from D3 and D5 for the treatment of refractory shock. It would thus be obvious for a skilled person to combine a DPP3 inhibitor with an angiotensin-receptor-agonist like angiotensin II in order to solve the problem. Claims 15-16 and 19-21 are not inventive.

4.3 Claims 11-12 and 22-24 differ from D2 in that additionally the level of pro-adrenomedullin is assessed and/ an anti-ADM antibody is administered. The problem to be solved is to provide an alternative method of diagnosis or method of treatment of refractory shock. Document D4 discloses the assessment of pro-adrenomedullin fragment for determining the outcome of the treatment with an anti-adrenomedullin antibody e.g. in septic shock. In view of the disclosure of D1 in combination with D4 a skilled person would have considered to assess the level of pro-adrenomedullin in addition to DPP3 and would have envisaged the treatment with an anti-adrenomedullin antibody. Claims 11-12 and 22-24 do not involve an inventive step.

Claims 10-12 and 13-23 do not meet the requirements of Art. 33(3) PCT.

5 **Re Item VI**

Certain documents cited

Document D1 is not state of the art as the priority date is valid.

Re Item VIII

Certain observations on the international application

6 The value of the "predetermined threshold" used in claims 1, 6-14 and 20-25 is not defined in the claims. It is thus not possible to assess the scope of the claims. Said claims do not meet the requirements of Art. 6 PCT.

7 The subject-matter of claims 6-12 is not clear in that said claims are directed to a method of diagnosis of refractory shock wherein the claims also relate to the treatment of a patient. The subject-matter of said claims is thus not clear.

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