The examination is being carried out on the **following application documents**

Description, Pages

1-99 as published

Sequence listings, SEQ ID NO

1-44 as published

Claims, Numbers

1-21 filed in electronic form on 17-10-2022

Drawings, Sheets

1/15-15/15 as published

1 Art. 123(2) EPC:

The amended claims are allowable under Art. 123(2) EPC.

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. 54 EPC):

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

3.2 Claims 13 is directed to a vasopressor for use in the treatment of patients having a DPP3 level below a 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 level of DPP3 below a threshold which is not further specified does not differ from the patients having refractory shock as disclosed in D3. Claim 13 lacks novelty in view of D3.

4 Inventive step (Art. 56 EPC):

4.1 Document D2 which is the closest prior art for claims 1 and 21 discloses that circulatory DPP3 in patients with severe sepsis and septic shock increases with the severity and the mortality risk. The claims differ in that refractory shock is diagnosed. It is considered that in view of D2 it would be obvious for a skilled person to determine the level of DPP3 in order to assess the risk of refractory shock the outcome of a treatment. Claims 1 and 21 do not involve an inventive step. The dependent claims 2-12 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to inventive step. The subject-matter of said claims appears to be obvious in view of D2.

4.2 Document D3 discloses the use of vasopressors e.g. arginine vasopressin for the treatment of refractory shock. Claim 14 differs in that a 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. Claim 14 is not inventive. The dependent claim 17 is also not inventive.

4.3 The dependent claims 15-16 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 are not inventive.

4.4 Claims 19-20 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 19-20 do not involve an inventive step.

5 Art. 84 EPC:

5.1 The value of the "predetermined threshold" is not defined in the claims. It is thus not possible to assess the scope of the claims. The argument that the physician will set the threshold by assessing DPP3 in different groups and set a threshold depending if the physician was prepared to accept more less false positives cannot be followed. The applicant considers that this would be a routine task for a physician. This argument cannot be followed. It is considered that the claims are more an invitation to perform a research program in order to determine the DPP3 levels which are indicative of a refractory shock. This would require a clinical study and would represent an undue burden for a skilled person. It is considered that claims 1, 13-14 and 21 do not meet the requirements of Art.84 EPC.

5.2 It is not clear which compounds fall in the scope of the functional definition "inhibitor of the activity of DPP3". Claim 14 does not meet the requirements of Art. 84 EPC.

5.3 Claim 18 seems to be dependent of claim 13 but refers to treatment with Angiotensin receptor agonists or DPP3 inhibitors whereas claim 13 is directed to vasopressors. This inconsistency renders the scope of the claim unclear.

5.4 It is not clear which compounds fall in the scope of the terms "precursor of Angiotensin receptor agonists in claims 15-16 and 18. Said claims lack clarity (Art. 84 EPC).

5.5 The dependent claims 2-12 should read "a method according to claim 1...". The dependent second medical use claims 15-20 should read e.g. "inhibitor of the activity of DPP3 for use according to claim...".

6 The applicant is invited to file new claims which take account of the above comments.

When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims. Care should be taken during revision, especially of the introductory portion and of any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).